Essential Med Notes

Comprehensive medical reference and review for the
United States Medical Licensing Exam Step 2 and
the Medical Council of Canada Qualifying Exam Part I

31st Edition

Editors-in-Chief:
Justin Hall and Azra Premji

Wherever the art of medicine is loved,
there is also a love of humanity.

– Hippocrates
**Note:**

Many of you have wondered about the *Toronto Notes* logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius’ healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

Thomas O’Brien, MD
Class of 2009
M.D. Program, University of Toronto
Dear Readers,

As Editors-in-Chief of Essential Med Notes 2015, we are proud to present the current edition.

First produced in 1985 from a set of study notes drafted by medical students at the University of Toronto, Toronto Notes and its international version, Essential Med Notes, have grown to be one of the premier study resources for generations of medical graduates in Canada and abroad. This rich history is rooted in our commitment to publish a student-edited, comprehensive study resource to serve students across clinical rotations and in preparation for the USMLE Step 2 and the Canadian MCCQE Part I.

For 30 years, we have remained committed to our original vision. With each successive edition, we strive to enhance the features of our print and online resources by listening to the feedback of our users. The focus of Essential Med Notes 2015 is to make medical knowledge accessible and retainable by distilling information into high-quality figures, tables, algorithms, and clinical pearls. This edition of Essential Med Notes offers new and exciting changes. We feature a consistent and easy-to-view layout across 30 chapters including the new Vascular Surgery chapter. Moreover, we have updated the text to reflect current best practice guidelines and clinically-relevant advances in medical research. As well, the text has been revised to reflect the new DSM-5 clinical guidelines. We are particularly excited to present the new accompanying Essential Med Notes Handbook. In response to user feedback, the Handbook has been streamlined to provide you with the most essential and up-to-date information on clinical scenarios commonly encountered while on the ward, in the clinic, or in the operating room. Finally, we have enhanced the Essential Med Notes eBook to include additional high-quality color images for a superior mobile learning experience.

Essential Med Notes 2015 is produced by Toronto Notes for Medical Students Inc., a non-profit organization supporting various medical student initiatives including community outreach programs and medical school clubs through the University of Toronto Medical Society, charitable events, and student bursaries and scholarships.

The production of this text would not have been possible without the commitment, energy, and passion of our dedicated team of over 150 students, artists, and faculty members at the University of Toronto's Faculty of Medicine as well as numerous faculty members at top-ranked U.S. institutions. We are grateful for the dedication and significant contributions of our lead editors: Amin Bahubeshi, Jillian Bardsley, Mandeep Pinky Gaidhu, Amanda Huynh, Jessica Huynh, Vahagn Karapetyan, Evan Lilly, Khaled Ramadan, and Karim Virani. We would also like to thank our Production Managers, Charles He and Ilya Mukovozov, for their hard work and efforts toward making this year’s edition a success. Our website team has been invaluable in improving our online resources to offer our users an enhanced electronic experience. We appreciate the creativity put forth by the Biomedical Communications artists in conceptualizing and developing numerous new illustrations as well as the innovative three-dimensional cover rendering. We would also like to acknowledge our partners at Type & Graphics, particularly Enrica Aguilera, for their continued guidance in the production of this text. Finally we would like to express our deepest gratitude to all previous Editors-in-Chief of Essential Med Notes.

We hope you find Essential Med Notes to be an indispensable resource. We encourage your feedback and place tremendous importance on making changes based on the user experience. On behalf of the 2015 editorial team, we wish you the best in your studies and hope that you will find Essential Med Notes 2015 a valuable asset to your success.

Sincerely,

Justin Hall, MSc, MPH and Azra Premji, MSc, RRT
Editors-in-Chief, Essential Med Notes 2015
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Acknowledgements

We would like to acknowledge the exceptional work of all previous *Essential Med Notes* and *Toronto Notes* (formerly MCCQE Notes) Editors-in-Chief and their editorial teams. The 2015 edition of this text was made possible with their contributions.

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How to Use This Book

This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of *Essential Med Notes 2015* allows easy identification of important information. These items are indicated by icons interspersed throughout the text:

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<th>Icon</th>
<th>Icon Name</th>
<th>Significance</th>
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<td><img src="image" alt="Key Objectives" /></td>
<td>Key Objectives</td>
<td>This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics.</td>
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<tr>
<td><img src="image" alt="Clinical Pearl" /></td>
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<td>This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text.</td>
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</tr>
<tr>
<td><img src="image" alt="Cross-Reference" /></td>
<td>Cross-Reference</td>
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<tr>
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</tr>
<tr>
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<td><img src="image" alt="Online Resources" /></td>
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<td>This icon is found next to headings in the text. It indicates topics that correspond with electronic resources such as Functional Neuroanatomy or ECGs Made Simple, available online (<a href="http://www.torontonotes.ca">www.torontonotes.ca</a>).</td>
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</table>

Chapter Divisions

To aid in studying and finding relevant material quickly, each chapter is organized in the following general framework:

**Basic Anatomy/Physiology Review**
- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

**Common Differential Diagnoses**
- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

**Diagnoses**
- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

**Common Medications**
- a quick reference section for review of medications commonly prescribed
## Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor
To convert from the SI unit to the conventional unit, **divide** by conversion factor

<table>
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<tr>
<th>Conventional Unit</th>
<th>Conversion Factor</th>
<th>SI Unit</th>
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<tbody>
<tr>
<td>ACTH</td>
<td>pg/mL</td>
<td>0.22 pmol/L</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/dL</td>
<td>10 g/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>mg/dL</td>
<td>17.1 µmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>mg/dL</td>
<td>0.25 mmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>mg/dL</td>
<td>0.0259 mmol/L</td>
</tr>
<tr>
<td>Cortisol</td>
<td>µg/dL</td>
<td>27.59 nmol/L</td>
</tr>
<tr>
<td>Creatinine</td>
<td>mg/dL</td>
<td>88.4 µmol/L</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>mL/min</td>
<td>0.0167 mL/s</td>
</tr>
<tr>
<td>Ethanol</td>
<td>mg/dL</td>
<td>0.217 mmol/L</td>
</tr>
<tr>
<td>Ferritin</td>
<td>ng/mL</td>
<td>2.247 pmol/L</td>
</tr>
<tr>
<td>Glucose</td>
<td>mg/dL</td>
<td>0.0555 mmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>%</td>
<td>0.01 proportion of 1.0</td>
</tr>
<tr>
<td>Hemaglobin</td>
<td>g/dL</td>
<td>10 g/L</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>mg/dL</td>
<td>0.0259 mmol/L</td>
</tr>
<tr>
<td>Iron, total</td>
<td>µg/dL</td>
<td>0.179 µmol/L</td>
</tr>
<tr>
<td>Lactate (lactic acid)</td>
<td>mg/dL</td>
<td>0.111 mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>mg/dL</td>
<td>0.0259 mmol/L</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>x 10⁴ cells/mm³</td>
<td>1 x 10⁹ cells/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>mg/dL</td>
<td>0.411 mmol/L</td>
</tr>
<tr>
<td>MCV</td>
<td>µm³</td>
<td>1 fL</td>
</tr>
<tr>
<td>Platelets</td>
<td>x 10³ cells/mm³</td>
<td>1 x 10⁹ cells/L</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>% of RBCs</td>
<td>0.01 proportion of 1.0</td>
</tr>
<tr>
<td>Salicylate</td>
<td>mg/L</td>
<td>0.00724 mmol/L</td>
</tr>
<tr>
<td>Testosterone</td>
<td>ng/dL</td>
<td>0.0347 nmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄)</td>
<td>ng/dL</td>
<td>12.87 pmol/L</td>
</tr>
<tr>
<td>Total Iron Binding Capacity</td>
<td>µg/dL</td>
<td>0.179 µmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃)</td>
<td>pg/dL</td>
<td>0.0154 pmol/L</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>mg/dL</td>
<td>0.0113 mmol/L</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>mg/dL</td>
<td>0.357 mmol/L</td>
</tr>
<tr>
<td>Uric acid</td>
<td>mg/dL</td>
<td>59.48 µmol/L</td>
</tr>
</tbody>
</table>

### Temperature Conversions

- **Celsius** → **Fahrenheit** \( F = (C \times 1.8) + 32 \)
- **Fahrenheit** → **Celsius** \( C = (F - 32) \times 0.5555 \)

### Weight Conversions

- **Kilograms** → **Pounds** 1 kg = 2.2 lbs
- **Pounds** → **Ounces** 1 lb = 16 oz
- **Ounces** → **Grams** 1 oz = 28.3 g
- **Inches** → **Centimetres** 1 in = 2.54 cm
## Commonly Measured Laboratory Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial Blood Gases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>PCO₂</td>
<td>35-45 mmHg</td>
<td>4.7-6.0 kPa</td>
</tr>
<tr>
<td>PO₂</td>
<td>80-105 mmHg</td>
<td>10.6-14 kPa</td>
</tr>
<tr>
<td><strong>Serum Electrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>22-28 mEq/L</td>
<td>22-28 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.4-10.2 mg/dL</td>
<td>2.1-2.5 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95-106 mEq/L</td>
<td>95-106 mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.3-2.1 mEq/L</td>
<td>0.65-1.05 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.7-4.5 mg/dL</td>
<td>0.87-1.45 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.0 mEq/L</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>136-145 mEq/L</td>
<td>136-145 mmol/L</td>
</tr>
<tr>
<td><strong>Serum Nonelectrolytes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5-5.0 g/dL</td>
<td>35-50 g/L</td>
</tr>
<tr>
<td>ALP</td>
<td>35-100 U/L</td>
<td>35-100 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Amylase</td>
<td>25-125 U/L</td>
<td>25-125 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Bilirubin (direct)</td>
<td>0-0.3 mg/dL</td>
<td>0-5 µmol/L</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>0.1-1.0 mg/dL</td>
<td>2.17 µmol/L</td>
</tr>
<tr>
<td>BUN</td>
<td>7-18 mg/dL</td>
<td>2.5-7.1 mmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/dL</td>
<td>&lt;5.2 mmol/L</td>
</tr>
<tr>
<td>Creatinine (female)</td>
<td>10-70 U/L</td>
<td>10-70 U/L</td>
</tr>
<tr>
<td>Creatinine (male)</td>
<td>25-90 U/L</td>
<td>25-90 U/L</td>
</tr>
<tr>
<td>Creatine Kinase – MB fraction</td>
<td>0-12 U/L</td>
<td>0-12 U/L</td>
</tr>
<tr>
<td>Ferritin (female)</td>
<td>12-150 ng/mL</td>
<td>12-150 µg/L</td>
</tr>
<tr>
<td>Ferritin (male)</td>
<td>15-200 ng/mL</td>
<td>15-200 µg/L</td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>70-110 mg/dL</td>
<td>3.8-6.1 mmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;6%</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>LDH</td>
<td>100-250 U/L</td>
<td>100-250 U/L</td>
</tr>
<tr>
<td>Osmolality</td>
<td>275-300 mOsm/kg</td>
<td>275-300 mOsm/kg</td>
</tr>
<tr>
<td><strong>Serum Hormones</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH (0800h)</td>
<td>&lt;60 pg/mL</td>
<td>&lt;13.2 pmol/L</td>
</tr>
<tr>
<td>Cortisol (0800h)</td>
<td>5-23 µg/dL</td>
<td>138-635 nmol/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>&lt;20 ng/mL</td>
<td>&lt;20 ng/mL</td>
</tr>
<tr>
<td>Testosterone (male, free)</td>
<td>9-30 ng/dL</td>
<td>0.31-1 pmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄)</td>
<td>5-12 ng/dL</td>
<td>64-155 nmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃)</td>
<td>115-190 ng/dL</td>
<td>1.8-2.9 nmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.5-5 µU/mL</td>
<td>0.5-5 µU/mL</td>
</tr>
<tr>
<td><strong>Hematologic Values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR (female)</td>
<td>0-20 mm/h</td>
<td>0-20 mm/h</td>
</tr>
<tr>
<td>ESR (male)</td>
<td>0-15 mm/h</td>
<td>0-15 mm/h</td>
</tr>
<tr>
<td>Hemoglobin (female)</td>
<td>12.3-15.7 g/dL</td>
<td>123-157 g/L</td>
</tr>
<tr>
<td>Hemoglobin (male)</td>
<td>13.5-17.5 g/dL</td>
<td>140-174 g/L</td>
</tr>
<tr>
<td>Hematocrit (female)</td>
<td>36-46%</td>
<td>36-46%</td>
</tr>
<tr>
<td>Hematocrit (male)</td>
<td>41-53%</td>
<td>41-53%</td>
</tr>
<tr>
<td>INR</td>
<td>0.0-1.1</td>
<td>0.0-1.1</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>4.5-11 x 10³ cells/mm³</td>
<td>4.5-11 x 10⁹ cells/L</td>
</tr>
<tr>
<td>MCV</td>
<td>88-100 µm⁢³</td>
<td>88-100 fL</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-400 x 10⁹/mm³</td>
<td>150-400 x 10⁹/L</td>
</tr>
<tr>
<td>PTT</td>
<td>25-35 s</td>
<td>25-35 s</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>0.5-1.5% of RBC</td>
<td>20-84 x 10⁹/L</td>
</tr>
</tbody>
</table>
American law applicable to medical practice varies between state jurisdictions and changes over time. Criminal law is nationwide, but non-criminal (civil) law varies between states. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.
The US Health Care System

Overview of US Health Care System

• the United States health care system is primarily market-based
• it is funded and delivered by a mixture of the public, private, and voluntary sectors; private-for-profit is the prevailing method of delivery
• public funding is derived from taxes raised at both the federal and state government levels

History

1901  American Medical Association established as the national organization of state and local medical groups

1929  Baylor Plan developed
• created by Dr. Justin Ford Kimball to ensure that teachers could pay their medical bills
• teachers pay 50 cents/mo in exchange for guarantee of medical services for 21 d

1930s  more hospitals adopt medical insurance plans as per the Baylor Plan

1939  Community hospitals work together to create health-care plans
• American Hospital Association (AHA) uses the term "Blue Cross" to describe health care plans that meet their standards
• emergence of prepaid plans covering physician and surgeon services

1946  Blue Shield created and represents physician sponsored health-care plans, which became the official designation for AHA health care plans in 1960

1954  Social Security coverage begins to include disability benefits

1965  Medicare and Medicaid programs introduced government funded health-care plans

1970s/1980s  • emergence of Health Maintenance Organizations (HMOs)
• HMOs offer managed care plans: health care packages that are provided by an HMO approved network of health care providers

1993  Universal health care system proposed but rejected by Congress

1996  Mental Health Parity Act passed
• invoked to decrease discrimination in health care coverage for mental health illnesses
• aggregate annual and lifetime limits for mental health services must match aggregate annual and lifetime limits for medical and surgical services

1996  Health Insurance Portability and Accountability Act passed
• Title 1: Health Care Access, Portability, and Renewability
  • provides protection of health care coverage to employees and their families if they change or lose their job
• Title 2: Preventing Health Care Fraud and Abuse; Administrative Simplification; Medical Liability Reform
  • addresses and establishes national standards for electronic health care transactions and security and privacy of health data

1997  State Children's Health Insurance Program (SCHIP) created
• states extend health coverage to uninsured children

1999  Ticket to Work and Work Incentives Improvement Act
• enables people with disabilities to be employed without affecting their Medicaid or Medicare coverage

2010  Affordable Care Act
• reform to health care to improve access to affordable health coverage and creates regulations on activities of private health insurance providers
Health Care Reform

- **Patient Protection and Affordable Care Act** and the **Health Care and Education Reconciliation Act** of 2010 are federal statutes signed into law in March 2010 that include a number of new health care provisions to be implemented over 8 yr:
  - expand Medicaid eligibility, provide subsidies for insurance premiums and incentives for businesses to provide health care benefits, prohibit denial of coverage/claims for pre-existing conditions, and establish health-insurance exchanges
  - costs are offset by a number of health care related taxes, including a tax penalty for citizens with no health insurance (low income persons and persons from a recognized religious sect are exempt)

Health Care Expenditure and Delivery in the US

- health care in the US represents a large economic sector
  - health care comprises over 17.9% of the gross domestic product (GDP) (highest in the OECD), amounting to $8,608 USD per capita in 2011
  - one advantage is the widespread availability of technology – the US has 4 times as many MRI machines per capita than Canada
- the US scores poorly on some indicators of population health, with a life expectancy below the OECD average and infant mortality above the OECD average; possible factors that account for this discrepancy are:
  - poor health of large uninsured population
  - high cost of health care administration
  - the provision of inefficient high-cost, high-intensity care
  - the higher-spending regions in the US do not provide any better quality of care, access to care, health outcomes, or satisfaction with care when compared to the lower-spending regions
- the US has the highest level of obesity of all OECD nations at 34.3%; this has major implications for future health care spending

Health Care Funding

- over 60% of healthcare provisions and spending come from universal programs such as Medicare, Medicaid, TRICARE, the Children's Health Insurance Program, and the Veterans Health Administration
- based on the total expenditure on health care, 31% goes to hospital care, 21% goes to physicians/clinical services, 10% to pharmaceuticals, 4% to dental, 6% to nursing homes, 3% to home health care, 3% for other retail products, 3% for government public health activities, 7% to administrative costs, 7% to investment, and 6% to other professional services

Health Care Delivery

- health care facilities are largely operated by the private sector
- it is estimated that approximately 62% of hospitals are non-profit, 20% are government owned, and 18% are for-profit

Access to Health Services

- 70% of Americans under the age of 65 have private health insurance, either employer-sponsored or individually purchased; 12% receive health care through public health insurance; 18%, mainly the poor, have no health insurance
- access to publicly funded health services occurs primarily through two programs, Medicare and Medicaid, which were created by the 1965 Social Security Act
- other federal government-funded health programs include the Military Health Services System, the Veterans Affairs Health Services System, the Indian Health Service, and the Prison Health Service
Table 1. Medicare and Medicaid Program Information

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Medicare</th>
<th>Medicaid</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;65 yr</td>
<td>People with end stage renal disease</td>
<td>People who receive funds through social assistance programs</td>
</tr>
<tr>
<td>People of any age meeting the Medicare definition of disability</td>
<td>Pregnant women</td>
<td>People with developmental disabilities</td>
</tr>
<tr>
<td>People of any age meeting the Medicare definition of disability</td>
<td>Low-income children through the 1997 State Children’s Health Insurance Program</td>
<td></td>
</tr>
<tr>
<td>Coverage</td>
<td>Basic “Part A” providing inpatient hospital care, home care, limited skilled nursing facility care, and hospice care</td>
<td>Basic coverage involves inpatient and outpatient hospital care, laboratory and x-ray services, skilled nursing care, home care, physician services, dental services, and family planning</td>
</tr>
<tr>
<td>Supplemental “Part B” covers outpatient physician and clinic services, and requires payment of a further monthly fee</td>
<td>Financing for Medicaid is provided jointly by the federal and state governments, and program details vary greatly between states</td>
<td></td>
</tr>
<tr>
<td>Co-payment</td>
<td>To help pay for out-of-pocket expenditures, and to cover many of the services not insured by Medicare, the majority of Medicare beneficiaries buy supplemental private health insurance</td>
<td>States may impose deductibles, coinsurance, or co-payments on some Medicaid recipients for certain services</td>
</tr>
<tr>
<td></td>
<td>Medicaid is not health insurance – coverage is unreliable as improvement in an individual’s financial status can lead to a loss of Medicaid eligibility</td>
<td></td>
</tr>
</tbody>
</table>


Ethical and Legal Issues in Medicine

Introduction to the Principles of Ethics

- ethics addresses
  1) principles and values that help define what is morally right and wrong
  2) rights, duties, and obligations of individuals and groups
- The practice of medicine assumes there is one code of professional ethics for all doctors and that they will be held accountable by that code and its implications

Table 2. The Four Principles of Medical Ethics

<table>
<thead>
<tr>
<th>Principle</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomy</td>
<td>Recognizes an individual’s right and ability to decide for himself/herself according to his/her beliefs and values</td>
</tr>
<tr>
<td></td>
<td>Not applicable in situations where informed consent and choice are not possible or may not be appropriate</td>
</tr>
<tr>
<td>Beneficence</td>
<td>The patient-based ‘best interests’ standard that combines doing good, avoiding harm, taking into account the patient’s values, beliefs, and preferences (so far as these are known)</td>
</tr>
<tr>
<td></td>
<td>Autonomy should be integrated with the physician’s conception of a patient’s medically-defined best interests</td>
</tr>
<tr>
<td></td>
<td>The aim is to minimize harmful outcomes and maximize beneficial ones</td>
</tr>
<tr>
<td></td>
<td>Paramount in situations where consent/choice is not possible or may not be appropriate</td>
</tr>
<tr>
<td>Non-Maleficence</td>
<td>Obligation to avoid causing harm; primum non nocere (“First, do no harm”)</td>
</tr>
<tr>
<td></td>
<td>A limit condition of the Beneficence principle</td>
</tr>
<tr>
<td>Justice</td>
<td>Fair distribution of benefits and harms within a community</td>
</tr>
<tr>
<td></td>
<td>Concept of fairness: Is the patient receiving what he/she deserves – his/her fair share? Is he/she treated the same as equally situated patients? How do one set of treatment decisions impact on others?</td>
</tr>
<tr>
<td></td>
<td>Respects basic human rights, such as freedom from persecution and the right to have one’s interests considered and respected</td>
</tr>
</tbody>
</table>

- the AMA has a Code of Medical Ethics
  - articulates the values of medicine as a profession and defines medicine’s integrity
  - source of the profession’s authority to self-regulate
  - evolving document that changes as new questions arise; AMA policy positions (“AMA Policy”) address current health care issues, the health care system, internal organizational structure, decision-making processes, and medical science and technology

Confidentiality

Overview of Confidentiality

- a full and open exchange of information between patient and physician is central to a therapeutic relationship
- privacy is the right of patients (which they may forego) while confidentiality is the duty of doctors (which they must respect barring patient consent or the requirements of the law)
• if inappropriately breached by a doctor, he/she can be sanctioned by the hospital, court, or regulatory authority
• based on the ethical principle of patient autonomy, patients have the right to the following:
  ▪ control of their own information
  ▪ the expectation that information concerning them will receive proper protection from unauthorized access by others (see Privacy of Medical Records)
  ▪ confidentiality may be ethically and legally breached in certain circumstances (i.e. the threat of harm to others)
  ▪ unlike the solicitor-client privilege, there is no ‘physician-patient privilege’ by which a physician, even a psychiatrist, can promise the patient absolute confidentiality
  ▪ physicians failing to abide by such regulations could be subject to professional or civil actions

Statutory Reporting Obligations
• legislation has defined specific instances where public interest overrides the patient right to confidentiality. These vary by state, but often include the following:
  1. suspected child or elder abuse or neglect – report to local child welfare authorities
  2. fitness to drive a vehicle or fly an airplane – report to Department of Motor Vehicles
  3. communicable diseases – report to public health authority and identifiable people at risk
  4. improper conduct of other physicians or health professionals – report to college or regulatory body of the health professional
  5. gunshot and knife wounds – notify police
  6. vital statistics must be reported; reporting varies by jurisdiction
• physicians who fail to report in these situations in the manner prescribed by state jurisdiction are subject to prosecution and penalty, and may be liable if a third party has been harmed

Duty to Protect/Warn
• the physician has a duty to protect the public from a known (or potential) dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detainment of violent patients for clinical assessment), informing the police, or warning the potential victim(s) if a patient expresses an intention to harm
• first established by a Supreme Court of California decision in 1976; known as the Tarasoff decision
• concerns of breaching confidentiality should not prevent the MD from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
• applies in a situation where:
  1. there is a clear risk to identifiable person(s);
  2. there is a risk of serious bodily harm or death; and
  3. the danger is imminent (i.e. more likely to occur than not)

Disclosure for Legal Proceedings
• disclosure of health records can be compelled by a court order, warrant, or subpoena

Privacy of Medical Records
• privacy of health information is protected by professional codes of ethics, legislation, and the physician’s fiduciary duty
• the legal duties of physicians involving patient confidentiality of medical records are outlined in the Health Insurance Portability and Accountability Act (HIPPA), which establishes principles for the collection, use, and disclosure of information that is part of commercial activity (i.e. physician practices, pharmacies, private labs)
• other aspects involving confidentiality are governed by state policy

Duties of Physicians with Regards to the Privacy of Health Information
• inform patients of information-handling practices through various means (i.e. posting notices, brochures and pamphlets, and/or through discussions with patients)
• obtain the patient’s expressed consent to disclose information to third parties
• provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
• provide secure storage of information and implement measures to limit access to patient records
• ensure proper destruction of information that is no longer necessary

Consent and Capacity

Ethical Principles Underlying Consent and Capacity
• consent is the autonomous authorization of a medical intervention by a patient
• usually, the principle of respect for patient autonomy overrides the principle of beneficence
• where a patient cannot make an autonomous decision (i.e. incapable), it is the duty of the SDM (or the physician in an emergency) to act on the patient’s known prior wishes or, failing that, to act in the patient’s best interests
• there is a duty to discover, if possible, what the patient would have wanted when capable
• central to determining best interests is understanding the patient's values, beliefs, and cultural or religious background
• more recently expressed wishes take priority over remote ones
• patient wishes may be verbal or written
• patients found incapable to make a specific decision should still be involved in that decision as much as possible
• agreement or disagreement with medical advice does not determine findings of capacity/incapacity
• however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed

Four Basic Requirements of Valid Consent
1. Voluntary
   - consent must be given free of coercion or pressure (i.e. from parents or other family members who might exert 'undue influence')
   - the physician must not deliberately mislead the patient about the proposed treatment
2. Capable
   - the patient must be able to understand and appreciate the nature and effect of the proposed treatment
3. Specific
   - the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (i.e. the patient must be informed if students will be involved in providing the treatment)
4. Informed
   - sufficient information and time must be provided to allow the patient to make choices in accordance with their wishes; information should include:
     • the nature of the treatment or investigation proposed and its expected effects
     • all significant risks and special or unusual risks
     • alternative treatments or investigations and their anticipated effects and significant risks
     • the consequences of declining treatment
     • risks that are common sense need not be disclosed (i.e. bruising after venipuncture)
     • answers to any questions the patient may have
     • the reasonable person test – the physician must provide all information that would be needed "by a reasonable person in the patient's position" to be able to make a decision
     • disclose common adverse events (>1/200 chance of occurrence) and serious risks (e.g. death) even if remote
     • it is the physician's responsibility to make reasonable attempts to ensure that the patient understands the information
     • physicians should not withhold information about a legitimate therapeutic option based on personal conscience (i.e. not discussing the option of emergency contraception)

Obtaining Legal Consent
• consent of the patient must be obtained before any medical intervention is provided; consent can be:
  • verbal or written, although written is usually preferred
    • a signed consent form is only evidence of consent – it does not replace the process for obtaining valid consent
    • what matters is what the patient understands and appreciates, not what the signed consent form states
  • implied (e.g. a patient holding out their arm for an immunization) or expressed
• consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm

Exceptions to Consent
1. Emergencies
   • treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their surrogate decision-maker (SDM)
   • emergency treatment should not violate a prior expressed wish of the patient (i.e. a signed Jehovah's Witness card)
   • if patient is incapable, MD must document reasons for incapacity and why situation is emergent
   • patients have a right to challenge a finding of incapacity as it removes their decision-making ability
   • if a SDM is not available, MD can treat without consent until the SDM is available or the situation is no longer emergent

Major Exceptions to Consent
• Emergencies
• Communicable diseases
• Mental health legislation
2. Legislation
- mental health legislation allowing for involuntary commitment is state governed. In general, an individual may be detained if he/she poses a threat to the self or others
- public health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases (see Population Health and Epidemiology, PH19)

3. Special Situations
- public health emergencies (i.e. an epidemic or communicable disease treatment)
- warrant for information by police

Consequences of Failure to Obtain Valid Consent
- treatment without consent is battery (an offense in tort), even if the treatment is life-saving (excluding situations outlined in exceptions section above)
- treatment of a patient on the basis of poorly informed consent may constitute negligence, also an offense in tort
- the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)

Consent
- treatment without consent = battery, including if NO consent or if WRONG procedure
- treatment with poor or invalid consent = negligence

Overview of Capacity
- capacity is the ability to
  - understand information relevant to a treatment decision
  - appreciate the reasonably foreseeable consequences of a decision or lack of a decision
- capacity is specific for each decision (i.e. a person may be capable to consent to having a chest x-ray, but not for a bronchoscopy)
- capacity can change over time (i.e. temporary incapacity secondary to delirium)
- a person is presumed capable unless there is good evidence to the contrary
- capable patients are entitled to make their own decisions
- capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny

Assessment of Capacity
- capacity assessments must be conducted by a physician and, if appropriate, in consultation with other health care professionals (e.g. another physician, a mental health nurse)
- clinical capacity assessment may include:
  - specific capacity assessment (i.e. capacity specific to the decision at hand)
    1. effective disclosure of information and evaluation of patient's reason for decision
    2. understanding of:
      - his/her condition
      - the nature of the proposed treatment
      - alternatives to the treatment
      - the consequences of accepting and rejecting the treatment
      - the risks and benefits of the various options
    3. for the appreciation needed for decision making capacity, a person must:
      - acknowledge the condition that affects him/herself
      - be able to assess how the various options would affect him or her
      - be able to reach a decision and adhere to it, and make a choice, not based primarily upon delusional belief (test: are their beliefs responsive to evidence?)
  - general impressions
  - input from psychiatrists, neurologists, etc.
- employ "Aid to Capacity Evaluation"
  - a decision of incapacity may warrant further assessment by psychiatrist(s) or the courts

Table 3. Aid to Capacity Evaluation

| Ability to understand the medical problem |
| Ability to understand the proposed treatment |
| Ability to understand the alternatives (if any) to the proposed treatment |
| Ability to understand the option of refusing treatment or of it being withheld or withdrawn |
| Ability to appreciate the reasonably foreseeable consequences of accepting the proposed treatment |
| Ability to appreciate the reasonably foreseeable consequences of refusing the proposed treatment |
| Ability to make a decision that is not substantially based on delusions or depression |

Adapted from Elchels E, et al. CMAJ 1996;155:657-661
Treatment of the Incapable Patient in a Non-Emergent Situation

- obtain informed consent from SDM
- criteria for detaining a patient against his/her will to receive treatment are state specific. In most circumstances, the physician must:
  - document assessment by psychiatrist or other qualified agent in chart
  - notify patient and agent verbally or in writing of assessment
  - if the patient objects to the determination, healthcare professionals cannot override the patient's wishes without obtaining a court order

Surrogate Decision-Makers (SDM)

- SDM are appointed if no living will or POA exists and must follow the following principles when giving informed consent:
  - act in accordance with wishes previously expressed by the patient while capable
  - if wishes unknown, act in the patient's best interest, taking the following into account:
    1. values and beliefs held by the patient while capable
    2. whether well-being is likely to improve with vs. without treatment
    3. whether the expected benefit outweighs the risk of harm
    4. whether a less intrusive treatment would be as beneficial as the one proposed
- the final decision of the SDM may and should be challenged by the MD if the MD believes the SDM is not abiding by the above principles

INSTRUCTIONAL ADVANCE DIRECTIVES

- allow patients to exert control over their care once they are no longer capable
- the patient sets out their decisions about future health care, including who they would allow to make treatment decisions on their behalf and what types of interventions they would want
- takes effect once the patient is incapable with respect to treatment decisions
- patients should be encouraged to review these documents with their family and physicians and to reevaluate them often to ensure they are current with their wishes

Powers of Attorney

- all Guardians and Attorneys have fiduciary duties for the dependent person

Definitions

- Power of Attorney for Personal Care
  - a legal document in which one person gives another the authority to make personal care decisions (health care, nutrition, shelter, clothing, hygiene, safety) on their behalf if they become mentally incapable
- Guardian of the Person
  - someone who is appointed by the Court to make decisions on behalf of an incapable person in some or all areas of personal care, in the absence of a POA for personal care
- Continuing Power of Attorney for Property
  - a legal document in which a person gives another the legal authority to make decisions about their finances if they become unable to make those decisions
- Guardian of Property
  - someone who is appointed by the Public Guardian and Trustee or the Courts to look after an incapable person's property or finances
- Public Guardian and Trustee
  - acts as a SDM of last resort on behalf of mentally incapable people who do not have another individual to act on their behalf
- Pediatric Aspects of Capacity
  - age of consent is state specific
  - physicians treating pediatric patients generally must obtain informed consent from a parent or a legal guardian
  - emancipated or mature minors may provide consent to their own medical care
  - infants and children are assumed to lack mature decision-making capacity for consent but they should still be involved (i.e. be provided with information appropriate to their comprehension level)
  - adolescents are usually treated as adults
  - preferably, assent should still be obtained from patient, even if not capable of giving consent
  - in the event that the physician believes the SDM is not acting in the child's best interest, an appeal must be made to the local child welfare authorities
  - under normal circumstances, parents have right of access to the child's medical record

When disagreements occur, institutional policies for timely conflict resolution should be followed, and may be followed by consultation with an ethics committee, pastoral service, or other counseling resource; resolution of disagreements in the courts should be pursued only as a last resort.
Negligence

**Ethical Basis**
- the doctor-patient relationship is formed on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
- negligence or malpractice is a form of failure on the part of the physician in fulfilling his/her fiduciary duty in providing appropriate care and leading to harm of the patient (and/or abuse of patient's trust)

**Legal Basis**
- physicians are legally liable to their patients for causing harm (tort) through a failure to meet the standard of care applicable under the circumstances
- standard/duty of care is defined as one that would reasonably be expected under similar circumstances of an ordinary, prudent physician of the same training, experience, specialization, and standing
- liability arises from physician's common law duty of care to his/her patients in the doctor/patient relationship
- action(s) in negligence (or civil liability) against a physician must be launched by a patient within a specific prescribed period required by the respective state in which the actions occurred

Truth-Telling

**Ethical Basis**
- helps to promote and maintain a trusting physician-patient relationship
- patients have a right to be told important information that physicians have regarding their care
- enables patients to make informed decisions about health care and their lives

**Legal Basis**
- required for valid patient consent (see Consent and Capacity, ELOAM5)
  - goal is to disclose information that a reasonable person in the patient's position would need in order to make an informed decision ("standard of disclosure")
- withholding information can be a breach of fiduciary duty and duty of care
- obtaining consent by using misleading information can be seen as negligent

**Evidence about Truth-Telling**
- most patients want to know what is wrong with them
- although many patients want to protect family members from bad news, they themselves would want to be informed in the same situation
- truth-telling improves compliance and health outcomes
- informed patients are more satisfied with their care
- negative consequences of truth-telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability

**Challenges in Truth-Telling**

**Medical Error**
- medical error may be defined as 'preventable adverse events' caused by the patient's medical care and not the patient's underlying illness. Some errors may be identified before they harm the patient, so not all error is truly ‘adverse’
  - serious adverse events (i.e. those resulting in death, hospitalization, or medical or surgical intervention) must be reported to the Food and Drug Administration (FDA)
- many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient's family and reported to the appropriate health authorities
- physicians should disclose to patients the occurrence of adverse events or errors caused by medical management, but should not suggest that they resulted from negligence because:
  - negligence is a legal determination
  - error is not equal to negligence
- disclosure allows the injured patient to seek appropriate corrective treatment promptly
  - physicians should avoid simple attributions as to cause and sole responsibility of others or oneself
  - physicians should offer apologies or empathic expressions of regret ("I wish things had turned out differently") as these can increase trust and are not admissions of guilt or liability

**Breaking Bad News**
- 'bad news' may be any information that reveals conditions or illnesses threatening the patient's sense of well-being
- caution patients in advance of serious tests about possible bad findings
• give warnings of impending bad news (see sidebar for example) and make sure you provide time for the patient
• poorly done disclosure may be as harmful as non-disclosure
• truth-telling may be a process requiring multiple visits
• adequate support should be provided along with the disclosure of difficult news
• SPIKES protocol was developed to facilitate “breaking bad news”

Arguments Against Truth-Telling
• may go against certain cultural norms and expectations
• may lead to patient harm and increased anxiety
• 10-20% of patients prefer not to be informed
• medical uncertainty may result in the disclosure of uncertain or inaccurate information

Exceptions to Truth-Telling
• patients may ‘waive’ the right to know: patient declines information that would normally be disclosed
• a patient may waive their right to know the truth about their situation when
  • the patient clearly declines to be informed
  • a strong cultural component exists that should be respected and acknowledged
  • the patient may wish others to be informed and make the medical decisions for him/her
  • the more weighty the consequences for the patient from non-disclosure, the more carefully one must consider the right to ignorance
• ‘Emergencies’: an urgent need to treat may legitimately delay full disclosure; the presumption is that most people would want such treatment and the appropriate SDM cannot be found
• ‘therapeutic privilege’
  • withholding information by the clinician in the belief that disclosure of the information would itself lead to severe anxiety, psychological distress, or physical harm to the patient
  • clinicians should avoid invoking therapeutic privilege due to its paternalistic overtones and is a defense of non-disclosure that is rarely accepted anymore
  • it is often not the truth that is unpalatable; it is how it is conveyed that can harm the patient

Ethical Issues in Health Care

Managing Controversial and Ethical Issues in Practice
• discuss in a non-judgmental manner
• ensure patients have full access to relevant and necessary information
• identify if certain options lie outside of your moral boundaries and refer to another physician if appropriate
• consult with appropriate ethics committees or boards
• protect freedom of moral choice for students or trainees

Reproductive Technologies

Overview of the Maternal-Fetal Relationship
• in general, maternal and fetal interests align
• in some situations, a conflict between maternal autonomy and the best interests of the fetus may arise

Ethical Issues and Arguments
• principle of reproductive freedom: women have the right to make their own reproductive choices
• coercion of a woman to accept efforts to promote fetal well-being is an unacceptable infringement of her personal autonomy

Legal Issues and Arguments
• the law upholds a woman’s right to life, liberty, and security of person and does not recognize fetal rights; key aspects of the mother’s rights include:
  • if a woman is competent and refuses medical advice, her decision must be respected even if the fetus will suffer
  • the fetus does not have legal rights until it is born alive and with complete delivery from the body of the woman
ART
- includes non-coital insemination, hormonal ovarian stimulation, and *in vitro* fertilization (IVF)
- topics with ethical concerns
  - donor anonymity vs. child-centered reproduction (i.e. knowledge about genetic medical history)
  - preimplantation genetic testing for diagnosis before pregnancy
  - use of new techniques without patients appreciating their experimental nature
  - access to ART
  - private vs. public funding of ART
  - social factors limiting access to ART (i.e. same-sex couples)
  - the 'commercialization' of reproduction

Fetal Tissue
- pluripotent stem cells can currently be derived from human embryonic and fetal tissue
- potential uses of stem cells in research
  - studying human development and factors that direct cell specialization
  - evaluating drugs for efficacy and safety in human models
  - cell therapy: using stem cells grown *in vitro* to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson's disease)
  - genetic treatment aimed at altering somatic cells (i.e. myocardial or immunological cells) is acceptable and ongoing

ART: Ethically Appropriate Actions
- educate patients and address contributors to infertility (e.g. stress, alcohol, medications, etc.)
- investigate and treat underlying health problems causing infertility
- wait at least 1 yr before initiating treatment with ART (exceptions – advanced age or specific indicators of infertility)
- educate and prepare patients for potential negative outcomes of ART

Induced Abortion
- induced abortion: the active termination of a pregnancy before fetal viability
- fetal viability: fetus >500 g or >20 wk gestational age

Prenatal/Antenatal Genetic Testing
- uses
  - to confirm a clinical diagnosis
  - to detect genetic predisposition to a disease
  - allows preventative steps to be taken and helps patient prepare for the future
  - gives parents the option to terminate a pregnancy or begin early treatment

- ethical dilemmas arise because of the sensitive nature of genetic information. Important considerations of genetic testing include:
  - the individual and familial implications
  - its pertaining to future disease
  - its ability to identify disorders for which there are no effective treatments or preventive steps
  - its ability to identify the sex of the fetus

- ethical issues and arguments regarding the use of prenatal/antenatal genetic testing include:
  - obtaining informed consent is difficult due to the complexity of genetic information
  - doctor’s duty to maintain confidentiality vs. duty to warn family members
  - risk of social discrimination (e.g. insurance) and psychological harm

- legal aspects
  - testing requires informed consent
  - no standard of care exists for clinical genetics but physicians are legally obligated to inform patients that prenatal testing exists and is available
  - where a genetic defect is found in the fetus, prospective parents may request or refuse an abortion
  - a physician is required to alert prospective parents when a potential genetic problem exists

Genetic Testing: Ethically Appropriate Actions
- thorough discussion and realistic planning with patient before testing is done
- genetic counseling for delivery of complex information
End-of-Life Care

Overview of Palliative and End-of-Life Care
• focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, and loved ones
• appropriate for any patient at any stage of a life-threatening illness
• may occur in a hospital, hospice, in the community, or at home
• often involves an interdisciplinary team of caregivers
• addresses the medical, psychosocial, and spiritual dimensions of care

Euthanasia and Physician-Assisted Suicide
• euthanasia: a deliberate act undertaken by one person with the intention of ending the life of another person to relieve that person’s suffering where the act is the cause of death
• physician-assisted suicide: the act of intentionally killing oneself with the assistance of a physician who deliberately provides the knowledge and/or the means

Common ethical arguments/opinions
• patient has right to make autonomous choices about the time and manner of own death
• belief that there is no ethical difference between the acts of euthanasia/assisted suicide and foregoing life-sustaining treatments
• belief that these acts benefit terminally ill patients by relieving suffering
• patient autonomy has limits
• death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death

Legal aspects
• in the United States, euthanasia is considered an illegal act
• physician-assisted suicide is currently only legal in the state of Oregon

Acceptable use of palliative and end-of-life care
• the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
• the appropriate withdrawal of life-support is distinguished from euthanasia and assisted suicide as it is seen as allowing the underlying disease to take its ‘natural course’
• refusals of care by the patient that may lead to death ought to be carefully explored by the physician to rule out any ‘reversible factors’ (poor palliation, depression, poverty, ill-education, isolation) that may be hindering authentic choice

Physician Responsibilities Regarding Death
• physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence
• coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
• in consultation with forensic pathologists and other specialists, the coroner establishes:
  • the identity of the deceased
  • where and when the death occurred
  • the medical cause of death
  • the means of death (i.e. natural, accidental, suicide, homicide, or undetermined)
• coroners do not make decisions regarding criminality or legal responsibility
• in a number of jurisdictions, any death not certified by the person’s physician must be referred to the medical examiner

Physician Competence and Professionalism

Legal Considerations
• physicians’ conduct and competence are legally regulated to protect patients and society via mandatory membership to governing bodies
• physicians are legally required to maintain a license with the appropriate authority and are thus legally bound to outlined policies on matters of conduct within his/her medical practice

Common Policies on Physician Conduct
• physicians must ensure that patients have access to continuous on-call coverage and are never abandoned
• sexual conduct with patients, even when consented to by the patient, is a serious matter that can lead to accusations of battery by the patient and college. Important notes on this topic include:
  ▪ inappropriate sexual conduct includes intercourse, undue touching, references to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
  ▪ in specified situations physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact
  ▪ physicians are permanently prohibited from personal relationships with patients whom they saw for psychotherapy
  ▪ physicians must maintain adequate records for each patient, which include:
    ▪ demonstration that care has been continuous and comprehensive
    ▪ minimal standards for record-keeping, including diagnosis, differential diagnosis, appropriate tests and referrals, coherent patient record
    ▪ records storage for 10 years in most jurisdictions
    ▪ although the medical record is the property of the physician or an institution, the patient or the patient’s delegate must be allowed full access to information in the medical record upon (usually written) request
  ▪ in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain adequate hospital records

AMA Guidelines for Impaired, Incompetent, or Unethical Colleagues
• Impairment: it may be necessary to report an impaired physician who continues to practice despite reasonable offers of assistance and referral to a hospital or state physician health program. The duty to report under such circumstances may entail reporting to the licensing authority
• Incompetence: initial reports of incompetence should be made to the appropriate clinical authority who would be empowered to assess the potential impact on patient welfare and to facilitate remedial action. The hospital peer review body should be notified where appropriate. Incompetence that poses an immediate threat to the health and safety of patients should be reported directly to the state licensing board
• Unethical conduct: unethical conduct that violates state licensing provision should be reported to the state licensing board. It is appropriate to report unethical conduct that potentially violates criminal statues to law enforcement authorities

Research Ethics
• involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
  ▪ study participants are protected
  ▪ clinical research is conducted to serve the interests of the participants and/or society as a whole
  ▪ major ethical dilemmas arise when a physician’s obligation to the patient comes into conflict with other obligations and incentives
  ▪ any exceptions to disclosure for therapeutic consent do not apply in an experimental situation

Ethical Considerations for Research Involving Human Subjects
• patient’s participation in research should not put him/her at a known or probable disadvantage with respect to medical care
• participant’s voluntary and informed choice is usually required
• participants should have access to the treatment that is considered standard
• scientists must employ a scientifically valid design to answer the research question
• scientists must demonstrate sufficient value to justify the risk posed to participants
• research must be conducted honestly (i.e. carried out as stated in the approved protocol)
• patients must not be enticed into risky research by the lure of money and investigators must not trade the interests of patients for disproportionate recompense by a sponsor

Physician-Industry Relations
• health care delivery in the United States involves collaboration between physicians and the pharmaceutical and health supply industries in the areas of research, education, and clinical evaluation packages (i.e. product samples)
• physicians have a responsibility to ensure that their participation in such collaborative efforts is in keeping with their duties to their patients and society
• AMA Guidelines on the acceptance of gifts or free products from industry include:
  ▪ any gifts accepted by physicians should primarily entail a benefit to patients and should not be of substantial value (e.g. textbooks as they serve a genuine educational function)
- cash payments should not be accepted
- individual gifts on minimal value are acceptable as long as they are related to the physician’s work
- appropriate disclosure of financial support or conflict of interest should be made at conferences and/or meetings
- subsidies to underwrite costs of continuing education conference or meetings are acceptable
- payments to defray costs of a conference should not be accepted directly by the physician attending a conference
- no gifts should be accepted if there are strings attached

### Resource Allocation

**Definition:** the distribution of goods and services to programs and people

- physicians have the duty to inform patients about therapeutic options even if they are not available
- physicians must make health care resources available to patients in a manner which is fair and equitable, without bias or discrimination
  - need and benefit are morally relevant criteria for resource allocation
  - gender, sexual orientation, religion, level of education, or age alone are morally irrelevant criteria
- ethical dilemmas can arise when deciding how best to allocate resources. Common ethical dilemmas include:
  - fair chances vs. best outcome: best outcome generally favoured vs. giving all patients fair access to limited resources (e.g. transplant list prioritization)
  - priorities problem: how much priority should the sickest patients receive?
  - aggregation problem: modest benefits to many vs. significant benefits to few
  - democracy problem: when to rely on a fair democratic process to arrive at a decision

### Guidelines for Appropriately Allocating Resources

- the physician’s primary obligation is to
  - protect and promote the welfare and best interests of his or her patients
  - choose interventions known to be beneficial on the basis of evidence of effectiveness
  - seek the tests or treatments that will accomplish the diagnostic or therapeutic goal for the least cost
  - advocate for one’s patients but avoid manipulating the system to gain unfair advantage for them
  - resolve conflicting claims for scarce resources justly, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures
  - inform patients of the impact of cost constraints on care, but in a sensitive way
  - seek resolution of unacceptable shortages at the level of hospital management or government

### AMA Policy on Resource Allocation

- physicians have the "duty to do all that [they] can for the benefit of the individual patient"
- decisions regarding the allocation of limited resources among patients should consider ethically appropriate criteria, which includes:
  - likelihood of benefit
  - urgency of need
  - changes in quality of life
  - duration of benefit
  - the amount of resources required for successful treatment

### Professional Considerations

#### Elderly Patient
- identify their resuscitation options (CPR or DNR), if applicable
- check for documentation of advance directives and POA where applicable
- for further details see ELOAM8

#### Pediatric Patient
- identify the primary decision-maker (parents, guardian, wards-of-state, emancipated)
- be wary of custody issues if applicable

#### Terminally Ill or Palliative Patient
- consider the SPIKES approach to breaking bad news
- what are their goals of care, i.e. disease vs. symptom management?
- identify advance directives, POA, or SDM, if applicable
- check for documentation of resuscitation options (CPR or DNR) and likelihood of success
- for further details, see Geriatric Medicine, GM12
Incapable Patient
• if not already present, perform a formal capacity assessment
• identify if the patient has a SDM or who has their POA

Conscientious Objection

Patients Refusing Treatment
• in accordance with the principle of autonomy, it is acceptable for competent patients to refuse medical interventions for themselves or others; exceptions may occur
• if parents or SDMs make decisions that are clearly not in the “best interests” of an incapable child, thereby risking mortality or serious morbidity, physicians may seek a court order to provide treatment against parental wishes
• in emergent scenarios, physicians may initiate treatment on the basis of legal precedent if withholding treatment places child at serious health risk
• in lower risk scenarios, such as refusing childhood immunization in a developed nation, there is a stronger obligation to respect the autonomy of the decision-makers

Physicians Refusing to Provide Treatment
• physicians may refuse to provide treatment or discontinue relationships with patients, but must ensure these patients can access services elsewhere
• for example, a pediatrician who refuses to treat an unvaccinated child should refer the family to another practice. In this case, it is recommended the pediatrician continue working with the family in the hopes that further education might help parents to make more informed decisions regarding their child's health

References

Bioethics

Governing Organizations

Health Care Delivery

Important Acts/Charters
Affordable Health Care for America Act (House bill – H.R. 3962).
America’s Healthy Future Act (Baucus bill – S. 1798).
Patient Protection and Affordable Care Act, 2010 (PL 111-148).
Health Insurance Portability and Accountability Act (PL 104-191).
Overview of Anesthesia

- anesthesia: lack of sensation/perception
- approach to anesthesia
  1. pre-operative assessment
  2. patient optimization
  3. plan anesthetic
  4. post-operative care

  - various types of anesthesia
  - pre-medications
  - airway management
  - monitors
  - induction
  - maintenance
  - extubation

Pre-Operative Assessment

Purpose
- identify patient's medical and surgical issues
- arrange further investigations, consultations and treatments for patients not yet optimized
- plan and consent for anesthetic techniques

History and Physical

History
- age, gender
- indication for surgery
- surgical/anesthetic Hx: previous anesthetics, any complications, previous intubations, medications, drug allergies, post-operative N/V
- FHx: abnormal anesthetic reactions, malignant hyperthermia, pseudocholinesterase deficiency
- PMHx
  - CNS: seizures, TIA/strokes, raised ICP, spinal disease, aneurysm
  - CVS: angina/CAD, MI, CHF, HTN, valvular disease, dysrhythmias, peripheral vascular disease (PVD), conditions requiring endocarditis prophylaxis, exercise tolerance, CCS/ NYHA class (see Cardiology and Cardiac Surgery, C34 for NYHA classification)
  - respiratory: smoking, asthma, COPD, recent upper respiratory tract infection, sleep apnea
  - GI: GERD, liver disease, NPO status
  - renal: insufficiency, dialysis, chronic kidney disease
  - hematologic: anemia, coagulopathies, blood dyscrasias
  - MSK: conditions associated with difficult intubations – arthritides (e.g. rheumatoid arthritis), cervical tumors, cervical infections/abscesses, trauma to cervical spine, previous cervical spine surgery, Trisomy 21, scleroderma, conditions affecting neuromuscular junction (e.g. myasthenia gravis)
  - endocrine: diabetes, thyroid disorders, adrenal disorders
  - other: morbid obesity, pregnancy, ethanol/other drug use

Physical Exam
- weight, height, BP, pulse, respiratory rate
- focused physical exam of the CNS, CVS, and respiratory systems
- general assessment of nutrition, hydration, and mental status
- airway assessment
  - done to determine intubation difficulty (no single test is specific or sensitive)
  - cervical spine stability and neck movement – upper cervical spine extension, lower cervical spine flexion (“sniffing position”)
  - Mallampati classification
  - “3-2-1 rule”
    - thyromental distance (distance of lower mandible in midline from the mentum to the thyroid notch): <3 finger breadths (<6 cm) is associated with difficult intubation
    - mouth opening (<2 finger breadths is associated with difficult intubation)
    - anterior jaw subluxation (<1 finger breadh is associated with difficult intubation)
  - tongue size
  - dentition, dental appliances/prosthetic caps, existing chipped/loose teeth – must inform patients of rare possibility of damage
  - nasal passage patency (if planning nasotracheal intubation)
  - assess difficulty of ventilation
  - examination of anatomical sites relevant to lines and blocks
    - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
    - sites for IV, central venous pressure (CVP), and pulmonary artery (PA) catheters
Pre-Operative Investigations

- routine pre-operative investigations are only necessary if there are comorbidities, or certain indications

Table 1. Suggested Indications for Specific Investigations in the Pre-Operative Period

<table>
<thead>
<tr>
<th>Test</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>Major surgery requiring group and screen or cросс and match; chronic cardiovascular, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelo suppression; patient less than 1 yr of age</td>
</tr>
<tr>
<td>Sickle Cell Screen</td>
<td>Genetically predisposed patient (hemoglobin electrophoresis if screen is positive)</td>
</tr>
<tr>
<td>INR, aPTT</td>
<td>Anticoagulant therapy, bleeding diathesis, liver disease</td>
</tr>
<tr>
<td>Electrolytes and Creatinine</td>
<td>HTN, renal disease, diabetes, pituitary or adrenal disease; digoxin, diuretic, or other drug therapies affecting electrolytes</td>
</tr>
<tr>
<td>Fasting Glucose Level</td>
<td>Diabetes (repeat on day of surgery)</td>
</tr>
<tr>
<td>Pregnancy (β-hCG)</td>
<td>Women of reproductive age</td>
</tr>
<tr>
<td>ECG</td>
<td>Heart disease, diabetes, other risk factors for cardiac disease; subarachnoid or intracranial hemorrhage, cerebrovascular accident, head trauma</td>
</tr>
<tr>
<td>Chest Radiograph</td>
<td>Cardiac or pulmonary disease, malignancy</td>
</tr>
</tbody>
</table>


Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality
Anesth 2005;102:257-268
Study: Case-control study of patients undergoing anesthesia.
Patients: 807 cases and 883 controls were analyzed among a cohort of 869,483 patients undergoing anesthesia between 1995-1997. Cases were defined as patients who either remained comatose or died within 24 h of receiving anesthesia. Controls were defined as patients who neither remained comatose nor died within 24 h of receiving anesthesia.
Intervention: General, regional, or combined anesthesia to patients undergoing a surgical procedure.
Main Outcome: Coma or death within 24 h of receiving anesthesia.
Results: The incidence of 24 h post-operative death was 8.8 per 10,000 anesthetics (95% CI 8.2-9.5) and the incidence of coma was 0.5 (95% CI 0.3-0.8). Anesthesia management risk factors that were associated with a decreased risk of morbidity and mortality were equipment check with protocol and documentation, directly available anesthesiologist with no change during anesthesia, 2 persons present at emergence of anesthesia, reversal of muscle relaxation, and post-operative pain medication.

American Society of Anesthesiology Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- ASA 1: a healthy, fit patient
- ASA 2: a patient with mild systemic disease
  - e.g. controlled type 2 diabetes mellitus (DM), controlled essential HTN, obesity, smoker
- ASA 3: a patient with severe systemic disease that limits activity
  - e.g. stable CAD, COPD, DM, obesity
- ASA 4: a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure
- ASA 5: a moribund patient not expected to survive 24 h without surgery
  - e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- ASA 6: declared brain dead, a patient whose organs are being removed for donation purposes
- for emergency operations, add the letter E after classification (e.g. ASA 3E)
Pre-Operative Optimization

- in general, prior to elective surgery
  - any fluid and/or electrolyte imbalance should be corrected
  - extent of existing comorbidities should be understood and these conditions should be optimized prior to surgery
  - medications may need to be adjusted

Medications

- pay particular attention to cardiac and respiratory medications, opioids and drugs with many side effects and interactions

  - pre-operative medications to consider
    - prophylaxis
      - risk of GE reflux: sodium citrate 30 mL PO or ranitidine 150-300 mg PO or metoclopramide 10 mg PO 30 min to 1 h pre-operatively
      - risk of infective endocarditis, GI/GU interventions: antibiotics
      - risk of adrenal suppression: steroid coverage
      - anxiety; consider benzodiazepines
      - COPD, asthma: bronchodilators
    - CAD risk factors: nitroglycerin and β-blockers

  - pre-operative medications to stop
    - oral hypoglycemics: stop on morning of surgery
    - antidepressants: stop on morning of surgery
    - ACE inhibitors and angiotension receptor blockers: stop on morning of surgery
    - warfarin (consider bridging with heparin), anti-platelet agents (e.g. clopidogrel)
    - discuss perioperative use of ASA, NSAIDs with surgeon
    - in patients undergoing noncardiac surgery, starting or continuing low-dosing aspirin in the perioperative period does not appear to protect against post-operative MI or death, but increases the risk of major bleeding
      - Note: this does not apply to patients with bare metal stents or drug-eluting coronary stents
    - pre-operative medication to adjust
      - insulin (consider insulin/dextrose infusion or holding dose), prednisone, bronchodilators

Hypertension

- BP <180/110 is not an independent risk factor for perioperative cardiovascular complications
- target sBP <180 mmHg, dBP <110 mmHg
- assess for end-organ damage and treat accordingly

Coronary Artery Disease

- ACC/AHA Guidelines (2007) recommend postponing elective surgery 4-6 wk following an MI
  - this period carries an increased risk of reinfarction/death
- if operative procedure is essential and cannot be delayed, invasive intra- and post-operative ICU monitoring reduces the risk of reinfarction
- mortality with perioperative MI is 20-50%
  - may 4 cardiac events and mortality (controversial, as recent data suggests ↑ stroke risk)
  - continue β-blocker if patient is routinely taking it prior to surgery
  - consider initiation of β-blocker in:
    - patients with CAD or indication for β-blocker
    - intermediate risk surgery, especially vascular surgery

Endocrine Disorders

- diabetes mellitus
  - clarify type I vs. type II
  - assess glucose control with history and HbA1c; well controlled diabetics have more stable glucose levels intraoperatively
  - end organ damage: be aware of damage to CVS, renal, and nervous systems, including autonomic neuropathy
  - formulate intraoperative glucose management plan based on type (I vs. II), glucose control, and extent of end organ damage
• hyperthyroidism
  ▪ can experience sudden release of thyroid hormone (thyroid storm)
  ▪ treatment: β-blockers and pre-operative prophylaxis
• adrenocortical insufficiency (Addison's, exogenous steroid use)
  ▪ consider intraoperative steroid supplementation

Respiratory Diseases

• smoking
  ▪ adverse effects: altered mucus secretion and clearance, decreased small airway caliber, and altered immune response
  ▪ abstain at least 8 wk pre-op if possible
  ▪ if unable, abstaining even 24 h pre-operatively has shown benefit
• asthma
  ▪ pre-operative management depends on degree of baseline asthma control
  ▪ increased risk of bronchospasm from intubation, delivery of desflurane
    ▪ administration of short course (up to 1 wk) pre-operative corticosteroids and inhaled β2-agonists decreases the risk of bronchospasm and does not increase the risk of infection, delayed wound healing
    ▪ avoid non-selective β-blockers; cardioselective β-blockers (metoprolol, atenolol) do not increase risk of bronchospasm in the short-term
  ▪ delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
  ▪ delay elective surgery by a minimum of 6 wks if patient develops URTI
• COPD
  ▪ anesthesia, surgery and analgesia predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation, and respiratory failure
  ▪ optimize with bronchodilators ± ICS ± antibiotics
  ▪ pre-operative ABG for all COPD stage II and III patients to assess baseline respiratory acidosis and plan post-operative management of hypercapnea
  ▪ cancel/delay elective surgery for acute exacerbation

Obesity and Obstructive Sleep Apnea

• assess for comorbid conditions in obese patient (independent risk factor for CVD, diabetes, OSA, cholelithiasis, HTN)
• previously undiagnosed conditions may require additional testing to characterize severity
• both obesity and OSA increase risk of difficult ventilation, intubation, and post-operative respiratory complications
  ▪ risk may be magnified with both diseases present

Hematological Disorders

• history of congenital or acquired conditions (sickle cell anemia, factor VIII deficiency, ITP, liver disease)
• evaluate hemoglobin, hematocrit and coagulation profiles when indicated (Table 1)
• anemia
  ▪ pre-operative treatments to increase hemoglobin (erythropoietin or pre-admission blood collection in certain populations)
• coagulopathies
  ▪ discontinue or modify anticoagulation therapies (warfarin, clopidogrel, ASA) in advance of elective surgeries
  ▪ administration of reversal agents if necessary: vitamin K, FFP, prothrombin complex concentrate, recombinant activated factor VII

Aspiration

• increased risk of aspiration with:
  ▪ decreased LOC
  ▪ trauma
  ▪ meals within 8 h
  ▪ suspected sphincter incompetence (GERD, hiatus hernia, nasogastric tube)
  ▪ increased abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
  ▪ laryngeal mask vs. endotracheal tube (ETT)
• management
  ▪ reduce gastric volume and acidity
  ▪ delay inhibiting airway reflexes with muscular relaxants
  ▪ employ rapid sequence induction (see Rapid Sequence Induction, A16)

## Fasting Guidelines

### Fasting Guidelines Prior to Surgery (American Society of Anesthesiologists)
- 8 h after a meal that includes meat, fried or fatty foods
- 6 h after a light meal (such as toast or crackers) or after ingestion of infant formula or non-human milk
- 4 h after ingestion of breast milk
- 2 h after clear fluids (water, black coffee, tea, carbonated beverages, juice without pulp)

## Monitoring

### Guidelines to the Practice of Anesthesia and Patient Monitoring
- an anesthetist present: “the only indispensable monitor”
- a completed pre-anesthetic checklist: including ASA class, NPO policy, Hx and investigations
- a perioperative anesthetic record: HR and BP every 5 min, dose and route of drugs and fluids
- continuous monitoring: see Routine Monitors for All Cases

### Routine Monitors for All Cases
- pulse oximeter, apparatus to measure BP, electrocardiography, capnography and temperature monitoring are required for general anesthesia and sedation (Ramsey Sedation Scale 4-6), agent-specific anesthetic gas monitor when inhalational anesthetic agents are used
- the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometer

### Elements to Monitor
- anesthetic depth
  ▪ inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing or sweating
  ▪ excessive: hypotension, bradycardia
- oxygenation: pulse oximetry, fraction of inspired O₂ (FiO₂)
- ventilation: verify correct position of ETT, chest excursions, breath sounds, ETCO₂ analysis, monitor inhaled and exhaled concentrations of inhaled anesthetics
- circulation: pulse, heart sounds, BP, telemetry, oximetry, CVP, pulmonary capillary wedge pressure
- temperature

---

**Figure 2. Typical anesthesia monitor**

Pre-Anesthetic Checklist
SAMMM
Suction: connected and working
Airways: laryngoscope and blades, ETT, syringe, stylet, oral and nasal airways, tape, bag, and mask
Machine: connected, pressures okay, all meters functioning, vaporizers full
Monitors: available, connected, and working
Medications: IV fluids and kit ready, emergency medicines in correct location and accessible
**Airway Management**

### Airway Anatomy

- Resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- Pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- Glottic opening (triangular space formed between the true vocal cords) is the narrowest segment of the laryngeal opening in adults
- The glottic opening is used as the space through which one visualizes proper placement of the ETT
- The trachea begins at the level of the thyroid cartilage, C6, and bifurcates into the right and left main bronchi at T4-T5 (approximately the sternal angle)

### Methods of Supporting Airways

1. Non-definitive airway (patent airway)
   - Jaw thrust/chin lift
   - Oropharyngeal and nasopharyngeal airway
   - Bag mask ventilation
   - Laryngeal mask airway
2. Definitive airway (patent and protected airway)
   - Endotracheal tube
   - Surgical airway (cricothyrotomy or tracheostomy)

#### Table 2. Methods of Supporting the Airway

<table>
<thead>
<tr>
<th>Bag and Mask</th>
<th>Laryngeal Mask Airway (LMA)</th>
<th>Endotracheal Tube (ETT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages/Indications</td>
<td>• Easy to insert</td>
<td>• Indications for intubation (5 Ps):</td>
</tr>
<tr>
<td></td>
<td>• Less airway trauma/irritation than ETT</td>
<td>• Patent airway</td>
</tr>
<tr>
<td></td>
<td>• Frees up hands (vs. face mask)</td>
<td>• Protects against aspiration</td>
</tr>
<tr>
<td></td>
<td>• Primarily used in spontaneously ventilating patient</td>
<td>• Positive pressure ventilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pulmonary toilet (suction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pharmacologic administration also hemodynamic instability</td>
</tr>
<tr>
<td>Disadvantages/Contraindications</td>
<td>• Risk of gastric aspiration</td>
<td>• Insertion can be difficult</td>
</tr>
<tr>
<td></td>
<td>• PPV &lt; 20 cm H2O needed</td>
<td>• Muscle relaxant usually needed</td>
</tr>
<tr>
<td></td>
<td>• Does not protect against laryngospasm or gastric aspiration</td>
<td>• Most invasive – see Complications During Laryngoscopy and Intubation, A9</td>
</tr>
<tr>
<td>Other</td>
<td>• Sizing by body weight (approx):</td>
<td>• Auscultate to avoid endobronchial intubation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-50 kg: 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-70 kg: 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70-100 kg: 5</td>
</tr>
</tbody>
</table>
| | • Facilitate airway patency with jaw thrust and chin lift | • Sizing (approx):
| | • Can use oropharyngeal/nasopharyngeal airway | Male: 8.0-9.0 mm |
| | | Female: 7.0-8.0 mm |
| | | Pediatric: (age/4) + 4 mm |
| | | Auscultate to avoid endobronchial intubation |
| | | Sizing (approx):

#### Tracheal Intubation

**Preparing for Intubation**

- Failed attempts at intubation can make further attempts more difficult due to tissue trauma
- Plan, prepare, and assess for potential difficulties (see Pre-Operative Assessment, A2)
- Ensure equipment is available and working (test ETT cuff, check laryngoscope light, machine check)
- Pre-oxygenate/denitrogenate: patient breathes 100% O2 for 3-5 min or for 4 vital capacity breaths
- May need to suction mouth and pharynx first

**Proper Positioning for Intubation**

- Align the three axes (mouth, pharynx, and larynx) to allow visualization from oral cavity to glottis
  - “Sniffing position”: flexion of lower C-spine (C5-C6), bow head forward, and extension of upper C-spine at atlanto-occipital joint (C1), nose in the air
- Contraindicated in known/suspected C-spine fracture/instability
- Proper position for laryngoscope tip to visualize cords is in epiglottic vallecula
Tube Insertion
• ETT insertion can incite a significant sympathetic response due to a "foreign body reflex" in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP, and coughing
• a malpositioned ETT is a potential hazard for the intubated patient
  ▪ if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
  ▪ if too shallow, may lead to accidental extubation, vocal cord trauma, or laryngeal paralysis as a result of pressure injury by the ETT cuff
• the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
  ▪ approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women

Confirmation of Tracheal Placement of ETT
• direct
  ▪ visualization of ETT passing through cords
  ▪ bronchoscopic visualization of ETT in trachea
• indirect
  ▪ EtCO2 in exhaled gas measured by capnography
  ▪ auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
  ▪ bilateral chest movement, condensation of water vapor in ETT visible during exhalation and no abdominal distention
  ▪ refilling of reservoir bag during exhalation
  ▪ CXR (rarely done): ETT tip at midpoint of thoracic inlet and carina (lateral CXR more sensitive and specific)
• esophageal intubation suspected when
  ▪ EtCO2 zero or near zero on capnograph
  ▪ abnormal sounds during assisted ventilation
  ▪ impairment of chest excursion
  ▪ hypoxia/cyanosis
  ▪ presence of gastric contents in ETT
  ▪ distention of stomach/epigastrium with ventilation
Complications During Laryngoscopy and Intubation
- dental damage
- laceration (lips, gums, tongue, pharynx, esophagus)
- laryngeal trauma
- esophageal or endobronchial intubation
- accidental extubation
- insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- laryngospasm (see Extubation, A18 for definition)
- bronchospasm

Difficult Airway
- difficulties with bag-mask ventilation, supraglottic airway, endotracheal intubation, infraglottic airway or surgical airway
- pre-operative assessment (history of previous difficult airway, airway examination) and pre-oxygenation are important preventative measures
- if difficult airway expected, consider
  - awake intubation
  - intubating with bronchoscope, trachlight (lighted stylet), fiber optic laryngoscope, glidescope, etc.
- if intubation unsuccessful after induction
  1. CALL FOR HELP
  2. ventilate with 100% O₂ via bag and mask
  3. consider returning to spontaneous ventilation and/or waking patient
- if bag and mask ventilation inadequate
  1. CALL FOR HELP
  2. attempt ventilation with oral airway
  3. consider/attempt LMA
  4. emergency invasive airway access (e.g. rigid bronchoscope, cricothyrotomy, or tracheostomy)

Oxygen Therapy
- in general, the goal of oxygen therapy is to maintain arterial oxygen saturation (SaO₂) >90%
- small decrease in saturation below SaO₂ of 90% corresponds to a large drop in arterial partial pressure of oxygen (PaO₂)
- in intubated patients, oxygen is delivered via the ETT
- in patients not intubated, there are many oxygen delivery systems available; the choice depends on oxygen requirements (FiO₂) and the degree to which precise control of delivery is needed
  - cyanosis can be detected at SaO₂ <85%, frank cyanosis at SaO₂ = 67%

Low Flow Systems
- acceptable if tidal volume 300-700 mL, respiratory rate (RR) <25, consistent ventilation pattern
- provide O₂ at flows between 0-10 L/min
- dilution of oxygen with room air results in a decrease in FiO₂
- an increase in minute ventilation (tidal volume x RR) results in a decrease in FiO₂
  - e.g. nasal canula (prong)
  - well tolerated if flow rates <5-6 L/min; drying of nasal mucosa at higher flows
  - nasopharynx acts as an anatomic reservoir that collects O₂
  - delivered oxygen concentration (FiO₂) can be estimated by adding 4% for every additional liter of O₂ delivered
  - provides FiO₂ of 24-44% at O₂ flow rates of 1-6 L/min

Reservoir Systems
- use a volume reservoir to accumulate oxygen during exhalation thus increasing the amount of oxygen available for the next breath
- simple face mask
  - covers patient’s nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore O₂ tubing at a rate of at least 6 L/min to ensure that exhaled CO₂ is flushed through the exhalation ports and not rebreathed
  - provides FiO₂ of 55% at O₂ flow rates of 10 L/min
- non-rebreather mask
  - a reservoir bag and a series of one-way valves prevent expired gases from re-entering the bag during the exhalation phase, the bag accumulates with oxygen
  - provides FiO₂ of 80% at O₂ flow rates of 10-15 L/min
Venturi mask  • 
• delivers specific FiO₂ by varying the size of air entrainment 
• oxygen concentration determined by mask's port and NOT the wall flow rate 
• enables control of gas humidity 
• FiO₂ ranges from 24-50%

Modes of Ventilation
• hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest 
• hypoxemic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt resistance) and underlying reason for mechanical ventilation 
• complications of mechanical ventilation 
  • airway complications 
    • tracheal stenosis, laryngeal edema 
    • alveolar complications 
    • ventilator-induced lung injury, ventilator-associated pneumonia (nosocomial pneumonia), barotrauma, volutrauma, inflammation, auto-PEEP, patient-ventilator asynchrony 
  • cardiovascular complications 
    • reduced venous return (secondary to increased intrathoracic pressure), reduced cardiac output, hypotension 
  • neuromuscular complications 
    • muscle atrophy 
    • increased intracranial pressure 
  • metabolic 
    • decreased CO₂ due to hyperventilation 
    • alkalemia with over correction of chronic hypercarbia

Ventilator Strategies
• mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation 
• hypoxemic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt 
• hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest 

High Flow Systems
• generate flows of up to 50-60 L/min 
• meet/exceed patient's inspiratory flow requirement 
• deliver consistent and predictable concentration of O₂ 
• Venturi mask
  • mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation 
• hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest 
• hypoxemic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt resistance) and underlying reason for mechanical ventilation 
• complications of mechanical ventilation 
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  • neuromuscular complications 
    • muscle atrophy 
    • increased intracranial pressure 
  • metabolic 
    • decreased CO₂ due to hyperventilation 
    • alkalemia with over correction of chronic hypercarbia

Ventilation
• ventilation is maintained with PPV in patients given muscle relaxants 
• assisted or controlled ventilation can also be used to assist spontaneous respirations in patients not given muscle relaxants as an artificial means of supporting ventilation and oxygenation 

Mechanical Ventilation
• indications for mechanical ventilation 
  • apnea 
  • hypventilation/acute respiratory acidosis 
  • intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg) 
  • required hyperventilation (to lower ICP) 
  • deliver positive end expiratory pressure (PEEP) 
  • increased intrathoracic pressure (e.g. laparoscopic procedure) 
• complications of mechanical ventilation 
  • airway complications 
    • tracheal stenosis, laryngeal edema 
    • alveolar complications 
    • ventilator-induced lung injury, ventilator-associated pneumonia (nosocomial pneumonia), barotrauma, volutrauma, inflammation, auto-PEEP, patient-ventilator asynchrony 
  • cardiovascular complications 
    • reduced venous return (secondary to increased intrathoracic pressure), reduced cardiac output, hypotension 
  • neuromuscular complications 
    • muscle atrophy 
    • increased intracranial pressure 
  • metabolic 
    • decreased CO₂ due to hyperventilation 
    • alkalemia with over correction of chronic hypercarbia

Modes of Ventilation
• assist-control ventilation (ACV) 
  • every breath is delivered with a pre-set tidal volume and rate or minute ventilation 
  • extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath 
• pressure control ventilation (PCV) 
  • a minimum frequency is set and patient may trigger additional breaths above the ventilator 
  • all breaths delivered at a preset constant inspiratory pressure 
• synchronous intermittent mandatory ventilation (SIMV) 
  • ventilator provides controlled breaths (either at a set volume or pressure) 
  • patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths 
• pressure support ventilation (PSV) 
  • patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure 
  • useful for weaning off ventilator 
• high-frequency oscillatory ventilation (HFOV) 
  • high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes 
  • used commonly in neonatal and pediatric respiratory failure 
  • used in adults when conventional mechanical ventilation is failing
non-invasive positive pressure ventilation (NPPV)
- achieved without intubation by using a nasal or face mask with
  - BiPAP: increased pressure (like PSV) on inspiration and lower constant pressure on expiration
  - CPAP: delivers constant pressure on both inspiration and expiration

Table 3. Causes of Abnormal CO₂ Levels

<table>
<thead>
<tr>
<th>Hypocapnea (Decreased CO₂)</th>
<th>Hypercapnea (Increased CO₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>Hyperventilation</td>
</tr>
<tr>
<td>Hypothermia (decreased metabolic rate)</td>
<td>Hyperthermia</td>
</tr>
<tr>
<td>Decreased pulmonary blood flow (decreased cardiac output)</td>
<td>Improved pulmonary blood flow after resuscitation or hypotension</td>
</tr>
<tr>
<td>Technical issues:</td>
<td>Technical issues:</td>
</tr>
<tr>
<td>Incorrect placement of sampling catheter</td>
<td>Water in capnography device</td>
</tr>
<tr>
<td>Inadequate sampling volume</td>
<td>Anesthetic breathing circuit error</td>
</tr>
<tr>
<td></td>
<td>• Inadequate fresh gas flow</td>
</tr>
<tr>
<td></td>
<td>• Rebreathing</td>
</tr>
<tr>
<td></td>
<td>• Exhausted soda lime</td>
</tr>
<tr>
<td></td>
<td>• Faulty circuit absorber valves</td>
</tr>
<tr>
<td>V/Q mismatch</td>
<td>Low bicarbonate</td>
</tr>
<tr>
<td>• Pulmonary thromboembolism</td>
<td></td>
</tr>
<tr>
<td>• Incipient pulmonary edema</td>
<td></td>
</tr>
<tr>
<td>• Air embolism</td>
<td></td>
</tr>
</tbody>
</table>

Intraoperative Monitoring

Temperature

Causes of Hypothermia (<36.0°C)
- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to:
  - OR environment (cold room, IV fluids, instruments)
  - open wound
  - prevent with inflated warming blanket and warmed IV fluids

Causes of Hyperthermia (>37.5-38.3°C)
- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- malignant hyperthermia (see Uncommon Complications, A26)
- over-zealous warming efforts

Heart Rate

Intraoperative Tachycardia
- tachycardia = HR >150 bpm; divided into narrow complex supraventricular tachycardias (SVT) or wide complex tachycardias
- SVT: sinus tachycardia, atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
- wide complex tachycardia: VT, SVT with aberrant conduction
- causes of sinus tachycardia:
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis
  - drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium)
  - Addisonian crisis, hypoglycemia, transfusion reaction, malignant hyperthermia
- for management of tachycardia, see ACLS Guidelines (Figure 16), A32
Intraoperative Bradycardia
• bradycardia = HR <50 bpm; most concerning are 2nd degree (Type 2 Mobitz) and 3rd degree heart block, which can both degenerate into asystole
• causes of sinus bradycardia
  ▪ increased parasympathetic tone vs. decreased sympathetic tone
  ▪ must rule out hypoxemia
  ▪ arrhythmias (see Cardiology and Cardiac Surgery, C15)
  ▪ baroreceptor reflex due to increased ICP or increased BP
  ▪ vagal reflex (oculocardiac reflex, carotid sinus reflex, airway manipulation)
  ▪ drugs (e.g. Sch, opioids, edrophonium, neostigmine, halothane, digoxin, β-blockers)
  ▪ high spinal/epidural anesthesia
• for management of bradycardia, see ACLS Guidelines (Figure 16), A32

Cardiac Arrest
• pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-shockable rhythms
  ▪ shockable: ventricular fibrillation (VF) and ventricular tachycardia (VT)
  ▪ non-shockable: asystole and pulseless electrical activity (PEA)
• for VF/VT, key to survival is good early CPR and defibrillation
• for asystole/PEA, key to survival is good early CPR and exclude all reversible causes
• reversible causes of PEA arrest (5 Hs and 5 Ts)
  ▪ 5 Hs: hypothermia, hypovolemia, hypoxia, hydrogen ions (acidosis), hypo/hyperkalemia
  ▪ 5 Ts: tamponade (cardiac), thrombosis (pulmonary), thrombosis (coronary), tension pneumothorax, toxins (overdose/poisoning)
• for management of cardiac arrest, see ACLS Guidelines (Figure 16), A32

Blood Pressure

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage Blood Loss</th>
<th>Percentage TBW Loss</th>
<th>Heart Rate</th>
<th>Blood Pressure</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0-15%</td>
<td>0-3%</td>
<td>&lt;100</td>
<td>Normal</td>
<td>Rapid infusion of 1-2 L of crystalloid (e.g. Ringer's lactate), maintenance fluids</td>
</tr>
<tr>
<td>II</td>
<td>15-30%</td>
<td>3-6%</td>
<td>&gt;100</td>
<td>Normal</td>
<td>Rapid infusion of 2 L of crystalloid and re-evaluate</td>
</tr>
<tr>
<td>III</td>
<td>30-40%</td>
<td>6-9%</td>
<td>&gt;120</td>
<td>Decreased</td>
<td>Rapid infusion of 2 L of crystalloid, replace losses with crystalloid (1:3) or pRBCs, colloid (1:1)</td>
</tr>
<tr>
<td>IV</td>
<td>&gt;40%</td>
<td>&gt;9%</td>
<td>&gt;140</td>
<td>Decreased</td>
<td>Rapid infusion of 2 L of crystalloid, replace losses with crystalloid (1:3) or pRBCs, colloid (1:1)</td>
</tr>
</tbody>
</table>

Note
- Goal is to maintain urine output at >0.5 mL/kg/h

Causes of Intraoperative Hypotension/Shock
• shock: condition characterized by inability of cardiovascular system to maintain adequate end-organ perfusion
  a) hypovolemic/hemorrhagic shock
    • most common form of shock, due to decrease in intravascular volume
  b) obstructive shock
    • obstruction of blood into or out of the heart
    • increased JVP, distended neck veins, increased systemic vascular resistance, insufficient cardiac output (CO)
    • e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism
  c) cardiogenic shock
    • myocardial dysfunction
    • increased JVP, distended neck veins, increased systemic vascular resistance, decreased CO
    • e.g. dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction
  d) septic shock
    • see Infectious Diseases, ID22
    • bacterial, viral, fungal, endotoxins/mediators cause vasodilation and capillary leakage
    • associated with contamination of open wounds, intestinal injury or penetrating trauma
    • signs: fever, decreased JVP, wide pulse pressure, increased CO, increased HR, decreased systemic vascular resistance ± pressors
    • initial treatment: antibiotics, volume expansion
  e) spinal/neurogenic shock
    • decreased sympathetic tone
    • hypotension without tachycardia or peripheral vasoconstriction (warm skin)
f) anaphylactic shock
  - acute/subacute generalized allergic reaction due to an inappropriate or excessive immune response (type 1 hypersensitivity)
  - treatment of anaphylactic shock
    - moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
      - epinephrine (1:1000) 0.3-0.5 mg SC
      - antihistamines: diphenhydramine (Benadryl®) 25-50 mg IM
      - salbutamol (Ventolin®) 1 cc via MDI
    - severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
      - ABCs, may need ETT due to airway edema
      - epinephrine (1:1000) 0.1-0.3 mg IV (or via ETT if no IV access) to start, repeat as needed
      - antihistamines: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg)
      - steroids: hydrocortisone 100 mg IV (~1.5 mg/kg) or methylprednisolone (Solumedrol®) 1 mg/kg IV q6h x 24 h
      - large volumes of crystalloid may be required

g) drugs
  - vasodilators, high spinal anesthetic interfering with sympathetic outflow

h) other
  - transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome
  - see Hematology, H54 and Endocrinology, E35, E22, E26

Causes of Intraoperative HTN
- inadequate anesthesia causing pain and anxiety
- pre-existing HTN, coarctation or preeclampsia
- hypoxemia/hypercarbia
- hypervolemia
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine)
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, thyroid storm, pheochromocytoma (see Endocrinology, E25, E36)

Fluid Balance and Resuscitation
- total requirement = maintenance + deficit + ongoing loss
- in surgical settings this formula must take into account multiple factors including pre-operative fasting/decreased fluid intake, increased losses during or before surgery, fluid shifting during surgery, fluids given with blood products and medications

What is the Maintenance?
- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (be aware of renal failure)
- 4:2:1 rule to calculate maintenance requirements (applies to crystalloids only)
  - 4 mL/kg/h first 10 kg
  - 2 mL/kg/h second 10 kg
  - 1 mL/kg/h for remaining weight >20 kg
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation, and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres, and CHF
- maintenance electrolytes
  - Na+: 3 mEq/kg/d
  - K+: 1 mEq/kg/d
- 50 kg patient maintenance requirements
  - fluid = 40 + 20 + 30 = 90 mL/h = 2160 mL/d = 2.16 L/d
  - Na+ = 150 mEq/d (therefore 150 mEq / 2.16 L/d = 69 mEq/L)
  - K+ = 50 mEq/d (therefore 50 mEq / 2.16 L/d = 23 mEq/L)
- above patient's requirements roughly met with 2/3 D5W, 1/3 NS
- 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per liter

What is the Deficit?
- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total Na+ content determines ECF volume; [Na+] determines ICF volume
• hypovolemia due to volume contraction
  ▪ extra-renal Na⁺ loss
    - GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - skin/respiratory: insensible losses (fever), sweating, burns
  ▪ vascular: hemorrhage
  ▪ renal Na⁺ and H₂O loss
  ▪ diuretics
  ▪ osmotic diuresis
  ▪ hypoaldosteronism
  ▪ salt-wasting nephropathies
  ▪ renal H₂O loss
  ▪ diabetes insipidus (central or nephrogenic)
  ▪ hypovolemia with normal or expanded ECF volume
    - decreased CO
    - redistribution
      - hypoalbuminemia: cirrhosis, nephrotic syndrome
      - capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
• replace water and electrolytes as determined by patient’s needs
• with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

<table>
<thead>
<tr>
<th>Table 5. Signs and Symptoms of Dehydration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Body Water Loss</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>3%</td>
</tr>
<tr>
<td>6%</td>
</tr>
<tr>
<td>9%</td>
</tr>
</tbody>
</table>

What are the Ongoing Losses?
• tubes
  ▪ Foley catheter, NG, surgical drains
• third-spacing (other than ECF, ICF)
  ▪ pleura, GI, retroperitoneal, peritoneal
  ▪ evaporation via exposed viscera, burns
• blood loss
• ongoing loss due to surgical exposure and evaporative losses

IV Fluids
• replacement fluids include crystalloid and colloid solutions
• IV fluids improve perfusion but NOT O₂ carrying capacity of blood

Initial Distribution of IV Fluids
• H₂O follows ions/molecules to their respective compartments

Crystalloid Infusion
• salt-containing solutions that distribute within ECF
• maintain euvoolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement)
• if large volumes are to be given, use balanced fluids such as Ringer’s lactate or Plasmalyte®, as too much normal saline (NS) may lead to hyperchloremic metabolic acidosis

Colloid Infusion
• includes protein colloids (albumin and gelatin solutions) and non-protein colloids (dextrans and starches e.g. hydroxyethyl starch [HES])
• distributes within intravascular volume
• 1:1 ratio (infusion:blood loss) only in terms of replacing intravascular volume
• HES colloids remain in intravascular space (metabolized by plasma serum amylase and renally excreted)
• the use of HES solutions is controversial because of recent RCTs and meta-analyses highlighting their renal and coagulopathic side effects, as well as a lack of specific indications for their use
• colloids are being used based on mechanistic and experimental evidence but there is a paucity of definitive studies investigating their safety and efficacy; routine use of colloids should be avoided

Colloids vs. Crystalloids for Fluid Resuscitation in Critically Ill Patients
Cochrane DB Syst Rev 2012;6:CD000567
Purpose: To evaluate the effects of colloids compared to crystalloids for fluid resuscitation, specifically when used in critically ill patients.
Methods: A meta-analysis was performed looking at randomized controlled trials comparing colloids vs. crystalloid use in patients requiring volume replacement. Pregnant women and neonates were excluded. Primary outcome was overall mortality.
Results: Results were broken down based on specific colloid. For albumin (or plasma protein fraction) the relative risk (RR) was 1.01 (95% CI 0.93-1.10) as compared to crystalloid. For hydroxyethyl starch the RR was 1.10 (95% CI 0.91-1.32). Modified gelatin had a RR of 0.91 (95% CI 0.49-1.72) and Dextran had a RR of 1.24 (95% CI 0.94-1.65). For colloids mixed in a hypertonic crystalloid as compared to isotonic crystalloid the RR was 0.88 (95% CI 0.71-1.06).
Conclusions: There is no evidence that use of colloids improves survival in trauma patients, burn patients, or post-operative patients when compared to crystalloid solutions. Given the increased cost of colloids as compared to crystalloids, it is recommended that crystalloids be the fluid of choice in these patients.
### Blood Products

- see Hematology, H52

#### Red Blood Cells (RBCs)
- 1U RBCs (approx. 300 ml) increases Hb by 10 g/L in a 70 kg patient
- RBCs may be diluted with colloid/crystalloid to decrease viscosity
- decision to transfuse based on initial blood volume, premorbid Hb level, present volume status, expected further blood loss, patient health status, patient consent
- massive transfusion ≥1 x blood volume/24 h

#### Autologous RBCs
- replacement of blood volume with one’s own RBCs
- may decrease complications (infectious, febrile, etc.)
- alternative to homologous transfusion in elective procedures, but only if adequate Hb and no infection
- pre-operative phlebotomy prior to elective surgery (up to 3U collected 3-5 wk before surgery)
- intraoperative salvage and filtration (cell saver); contraindicated in contaminated (e.g. bowel, abscess) or cancer cases

#### Non-RBC Products
- fresh frozen plasma (FFP)
  - contains all plasma clotting factors and fibrinogen close to normal plasma levels
  - to prevent/treat bleeding due to coagulation factor depletion/deficiencies, liver impairment
- cryoprecipitate
  - contains Factors VIII and XIII, von Willebrand Factor (vWF), fibrinogen
- platelets
  - used in thrombocytopenia, massive transfusions, impaired platelet function
- albumin
  - selective intravascular volume expander
- erythropoietin
  - can be used pre-operatively to stimulate erythropoiesis

#### Complications Due to Transfusion
- infectious risks: HIV, hepatitis B/C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), brucellosis, malaria, salmonellosis, measles, syphilis
- hypervolemia
- electrolyte changes: increased K+ in stored blood
- dilutional coagulopathy
- dilutional thrombocytopenia
- hypothermia
- citrate toxicity
- hypocalcemia
- iron overload
- transfusion-related immunosuppression: perioperative transfusion may be associated with increased risk of post-operative infection, increased short-term mortality and possible cancer recurrence
- see Hematology, H54 for list of transfusion reactions

### Table 6. IV Fluid Solutions

<table>
<thead>
<tr>
<th></th>
<th>ECF</th>
<th>Ringer’s Lactate</th>
<th>0.9% NS</th>
<th>0.45% NS in DSW</th>
<th>DSW</th>
<th>2/3 DSW + 1/3 NS</th>
<th>PlasmaLyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEq/L Na⁺</td>
<td>142</td>
<td>130</td>
<td>154</td>
<td>77</td>
<td>-</td>
<td>51</td>
<td>140</td>
</tr>
<tr>
<td>mEq/L K⁺</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
</tr>
<tr>
<td>mEq/L Ca²⁺</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>mEq/L Mg²⁺</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>mEq/L Cl⁻</td>
<td>103</td>
<td>109</td>
<td>154</td>
<td>77</td>
<td>-</td>
<td>51</td>
<td>98</td>
</tr>
<tr>
<td>mEq/L HCO₃⁻</td>
<td>27</td>
<td>28</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Colloid HES Solutions

<table>
<thead>
<tr>
<th></th>
<th>Concentration</th>
<th>Plasma Volume Expansion</th>
<th>Duration (h)</th>
<th>Maximum Daily Dose (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hespan®</td>
<td>6%</td>
<td>1:1</td>
<td>4-6</td>
<td>30-50</td>
</tr>
<tr>
<td>Pentaspan®</td>
<td>10%</td>
<td>1:1.2-1.5</td>
<td>18-24</td>
<td>28</td>
</tr>
</tbody>
</table>

### Calculating Acceptable Blood Losses (ABL)

- Blood volume
  - term infant 80 mL/kg
  - adult male 70 mL/kg
  - adult female 60 mL/kg

- Calculate estimated blood volume (EBV) (e.g. in a 70 kg male, approx. 70 mL/kg)
  - EBV = 70 kg x 70 mL/kg = 4900 mL

- Decide on a transfusion trigger, i.e. the Hb level at which you would begin transfusion, (e.g. 70 g/L for a person with Hb₁(0) = 150 g/L)
  - Hb(0) = 70 g/L

- Calculate ABL = Hct₁(0) – Hct(H) x EBV
  - Hct₁(0) = 150 – 70 x 4900
  - = 2613 mL

- Therefore in order to keep the Hb level above 70 g/L, RBCs would have to be given after approximately 2.6 L of blood has been lost

### Transfusion Infection Risks

<table>
<thead>
<tr>
<th>Virus</th>
<th>Risk per 1 unit pRBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 8-12 million</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1 in 5-7 million</td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1 in 1-1.7 million</td>
</tr>
<tr>
<td>HTLV</td>
<td>1 in 1-1.3 million</td>
</tr>
<tr>
<td>Syphilis</td>
<td>&lt;1 in 100 million</td>
</tr>
<tr>
<td>West Nile virus</td>
<td>No cases since 2003</td>
</tr>
</tbody>
</table>

### A Multicentre, Randomized, Controlled Clinical Trial of Transfusion Requirements in Critical Care

**Purpose**: To determine whether a restrictive strategy of RBC transfusion and a liberal strategy produce equivalent results in critically ill patients.

**Study**: Randomized controlled trial with 85-d follow-up.

**Patients**: 1,329 critically ill patients with sepsis after initial treatment who had Hb concentrations of <90 g/L within 72 h after admission to the ICU.

**Mean age**: 57.5 yr; 62.5% male.

**Intervention**: Patients were randomly assigned to either a restrictive strategy of transfusion, in which RBCs were transfused if the Hb dropped <70 g/L, or a liberal strategy, in which transfusions were given when the Hb dropped <100 g/L and Hb concentrations were maintained between 70-90 g/L.

**Main Outcomes**: All cause mortality rates at 30 d and 60 d, mortality rates during the stay in ICU and hospitalization, survival times during the first 30 d, and rates of organ failure and dysfunction.

**Results**: Overall, 30 d mortality was similar in the two groups. However, the rates were significantly lower with the restrictive strategy of RBC transfusion and a liberal strategy produce equivalent results in critically ill patients.

**Conclusions**: With the possible exception of patients with acute MI and unstable angina, a restrictive strategy of RBC transfusion is as effective as, and possibly superior to, a liberal transfusion strategy in critically ill patients.
**Types of Anesthesia**

- **general**
  - general anesthesia (GA)
  - total IV anesthesia (TIVA)

- **regional**
  - spinal, epidural
  - peripheral nerve block
  - IV regional

- **local**
  - local infiltration
  - topical

- **sedation**
  - monitored anesthesia care
  - note that different types of anesthesia can be combined (general + regional)

**General Anesthesia**
- induction, maintenance and extubation

---

**Induction**

**Routine Induction vs. Rapid Sequence Induction**

- routine induction is the standard in general anesthesia, however a RSI is indicated in patients at risk of regurgitation/aspiration (see Aspiration, A5)
- RSI uses pre-determined doses of induction drugs given at set times

**Table 8. Comparison of Routine Induction vs. RSI**

<table>
<thead>
<tr>
<th>Steps</th>
<th>Routine Induction</th>
<th>RSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equipment Preparation</td>
<td>Check equipment, drugs, suction, and monitors; prepare an alternative laryngoscope blade and a second ETT tube one size smaller</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy</td>
</tr>
<tr>
<td>2. Pre-Oxygenation/Denitrogenation</td>
<td>100% O₂ for 3 min or 4 vital capacity breaths</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation; if possible, give 3 min prior to laryngoscopy, but can skip this step in an emergent situation</td>
</tr>
<tr>
<td>3. Pre-Treatment Agents</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation; if possible, give 3 min prior to laryngoscopy, but can skip this step in an emergent situation</td>
</tr>
<tr>
<td>4. Induction Agents</td>
<td>Use IV or inhalation induction agent of choice</td>
<td>Use pre-determined dose of fast acting induction agent of choice</td>
</tr>
<tr>
<td>5. Muscle Relaxants</td>
<td>Muscle relaxant of choice given after the onset of the induction agent</td>
<td>Pre-determined dose of fast acting muscle relaxant (e.g. SCh) given IMMEDIATELY after induction agent</td>
</tr>
<tr>
<td>6. Ventilation</td>
<td>Bag-mask ventilation</td>
<td>DO NOT bag ventilate – can increase risk of aspiration</td>
</tr>
<tr>
<td>7. Cricoid Pressure</td>
<td>Backwards upwards rightwards pressure (BURP) to assist visualization if indicated</td>
<td>Sellick maneuver, also known as cricoid pressure, to prevent regurgitation and assist in visualization (2 kg pressure with drowsiness, 3 kg with loss of consciousness)</td>
</tr>
<tr>
<td>8. Intubation</td>
<td>Intubate, inflate cuff, confirm ETT position</td>
<td>Intubate once paralyzed (~45 s after SCh given), inflate cuff, confirm ETT position, cricoid pressure maintained until ETT cuff inflated and placement confirmed</td>
</tr>
</tbody>
</table>

**Induction Agents**

- induction in general anesthesia may be achieved with intravenous agents, volatile inhalation agents, or both

**Intravenous Agents**

- see Table 11, A27
- IV induction agents are non-opioid drugs used to provide amnesia and blunt reflexes
- these are initially used to draw the patient into the maintenance phase of general anesthesia rapidly, smoothly and with little adverse effects
  - examples include propofol, sodium thiopental (not available in North America), or ketamine
  - a continuous propofol infusion may also be used for the maintenance phase of GA

---

**Solubility of Volatile Anesthetics in Blood**

- Least Soluble to Most Soluble
  - Nitrous oxide < desflurane < sevoflurane < isoflurane < halothane
Volatile Inhalational Agents
- examples include sevoflurane, desflurane, isoflurane, enflurane, halothane, and nitrous oxide
- see Table 14, A28

MAC (Minimum Alveolar Concentration)
- the alveolar concentration of a volatile anesthetic at one atmosphere (atm) of pressure that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- 1.2-1.3 times MAC will often ablate response to stimuli in the general population
- potency of inhalational agents is compared using MAC
- MAC values are roughly additive when mixing N₂O with another volatile agent; however, this only applies to movement, not other effects such as BP changes (e.g. 0.5 MAC of a potent agent + 0.5 MAC of N₂O = 1 MAC of potent agent)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation, generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli, generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command, usually 0.3-0.4 of the usual MAC value

Muscle Relaxants and Reversing Agents

Muscle Relaxants
- two types of muscle relaxants
  1. depolarizing muscle relaxants: succinylcholine (SCh)
  2. non-depolarizing muscle relaxants: rocuronium, mivacurium, vecuronium, cistracurium, pancuronium
- see Tables 15 and 16, A29 for more details including mechanism of action
- block nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- never use muscle relaxants without adequate preparation and equipment to maintain airway and ventilation
- muscle relaxation produces the following desired effects
  1. facilitates intubation
  2. assists with mechanical ventilation
  3. prevents muscle stretch reflex and decreases muscle tone
  4. allows access to the surgical field (intracavitary surgery)
  5. nerve stimulator (i.e. train of four) is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade

Determinants of Speed of Onset of Volatile Anesthetics
- Solubility: decrease solubility → increase rate of induction
- Cardiac output (CO): as CO increases, anesthetic uptake to blood increases and alveolar gas concentration decreases, thus delaying induction
- Partial pressure difference between alveolar and venous blood: increase gradient → decrease rate of induction
- Inspired gas concentration: increase inspired concentration → increase rate of induction
- Alveolar ventilation: increase alveolar ventilation → increase rate of induction
- Second gas effect: when 2 gases are administered together, uptake of the first gas (e.g. N₂O) increases the alveolar concentration of the second gas (e.g. desflurane), increasing rate of induction
Reversing Agents
- neostigmine, pyridostigmine, edrophonium (see Table 17, A30)
- reversal agents are acetylcholinesterase inhibitors
  - inhibits enzymatic degradation of ACh; increases amount of ACh at nicotinic and muscarinic receptors, displacing non-depolarizing muscle relaxant
  - administer reversal agents when there has been some recovery of blockade (i.e. muscle twitch)
  - can only reverse the effect of non-depolarizing muscle relaxants
- anticholinergic agents (e.g. atropine, glycopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation and increased bowel peristalsis)

Analgesia
- options include opioids (e.g. morphine, fentanyl, hydromorphone), NSAIDS, acetaminophen, local, and regional anesthetic (see Table 12, A28)

Maintenance
- general anesthesia is maintained using volatile inhalation agents and/or IV agents (i.e. propofol infusion)
- analgesia (usually IV opioids) and muscle relaxants are also given as needed

Extubation
- criteria
  - patient must no longer have intubation requirements (see Table 2, A7)
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- general guidelines
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - allow ventilation (spontaneous or controlled) with 100% O₂ for 3-5 min
  - suction secretions from pharynx
  - deflate cuff, remove ETT on inspiration (vocal cords abducted)
  - ensure patient is breathing adequately after extubation
  - ensure face mask for O₂ delivery available
  - proper positioning of patient during transfer to recovery room (supine, head elevated)

Complications of Extubation
- early extubation
  - aspiration
  - laryngospasm
- late extubation
  - transient vocal cord incompetence
  - edema (glottic, subglottic)
  - pharyngitis, tracheitis

Laryngospasm
- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (by oropharyngeal secretions, blood, extubation)
- causes partial or total airway obstruction
- more likely to occur in semi-conscious patients
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: bag-mask ventilation with 100% oxygen, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose succinylcholine (0.25-1 mg/kg) and reintubation if hypoxia develops
Regional Anesthesia

- local anesthetic agent (LA) applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) for the purpose of reducing or preventing impulse transmission
- no CNS depression (unless overdose of local anesthetic); patient remains conscious
- regional anesthetic techniques categorized as follows:
  - epidural and spinal anesthesia (neuraxial anesthesia)
  - peripheral nerve blocks
  - IV regional anesthesia (e.g. Bier block)

Patient Preparation
- sedation may be indicated before block
- monitoring should be as extensive as for general anesthesia

Relative Indications for Regional Anesthesia
- patient preference
- superior postoperative analgesia
- decreased incidence of PONV
- shorter recovery and improved rehabilitation
- general anesthesia not available/contraindicated
- differential blockade (to block pain but preserve motor function)

Complications of Regional Anesthesia
- failure of technique/inadequate anesthesia
- unintentional total spinal anesthesia
- systemic drug toxicity due to overdose or intravascular injection (see Local Anesthesia, A21)
- injury to nerve root/spinal cord (nerve deficit), epidural vein (hematoma), peripheral nerve (intraneural injection)
- infection (e.g. osteitis, epidural abscess, meningitis)

Epidural and Spinal Anesthesia

- most useful for surgeries performed below level of umbilicus

Anatomy of Spinal/Epidural Area
- spinal cord extends to L2, dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

Table 9. Epidural vs. Spinal Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deposition Site</td>
<td>LA injected in epidural space (space between ligamentum flavum and dura)</td>
<td>LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots</td>
</tr>
<tr>
<td>Onset</td>
<td>Significant blockade requires 10-15 min</td>
<td>Rapid blockade (onset in 2-5 min)</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>Effectiveness of blockade can be variable</td>
<td>Very effective blockade</td>
</tr>
<tr>
<td>Difficulty</td>
<td>Technically more difficult; greater failure rate</td>
<td>Easier to perform due to visual confirmation of CSF flow</td>
</tr>
<tr>
<td>Patient Positioning</td>
<td>Position of patient not as important; specific gravity not an issue</td>
<td>Hyperbaric LA solution – position of patient important</td>
</tr>
</tbody>
</table>

Benefits of Regional Anesthesia
- Reduced perioperative pulmonary complications
- Reduced perioperative analgesia requirements
- Decreased PONV
- Reduced perioperative blood loss
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE

Epidural and Spinal Anesthesia

Anatomy of Spinal/Epidural Area

Spinous processes should be maximally flexed
L4 spinal processes found between iliac crests
Common sites of insertion are L3-L4 and L4-L5

Landmarking Epidural/Spinal Anesthesia

Spinous processes should be maximally flexed
L4 spinal processes found between iliac crests
Common sites of insertion are L3-L4 and L4-L5

Figure 9. Landmarks for placement of epidural/spinal

Table 9. Epidural vs. Spinal Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
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</tr>
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</tr>
</tbody>
</table>
Table 9. Epidural vs. Spinal Anesthesia (continued)

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific Gravity/Spread</td>
<td>Epidural injections spread throughout the potential space; specific gravity of solution does not affect spread</td>
<td>LA solution may be made hyperbaric (of greater specific gravity than the cerebrospinal fluid by mixing with 10% dextrose, thus increasing spread of LA to the dependent (low) areas of the subarachnoid space)</td>
</tr>
<tr>
<td>Dosage</td>
<td>Larger volume/dose of LA (usually &gt; toxic IV dose)</td>
<td>Smaller dose of LA required (usually &lt; toxic IV dose)</td>
</tr>
<tr>
<td>Continuous Infusion</td>
<td>Use of catheter allows for continuous infusion or repeat injections</td>
<td>None</td>
</tr>
<tr>
<td>Complications</td>
<td>Failure of technique, Hypotension, Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), e.g. &quot;high spinal&quot;</td>
<td>Failure of technique, Hypotension, Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), e.g. &quot;high spinal&quot;</td>
</tr>
<tr>
<td></td>
<td>Epidural or subarachnoid hematoma, Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications)</td>
<td>Epidural or subarachnoid hematoma, Post-spinal headache (CSF leak)</td>
</tr>
<tr>
<td></td>
<td>Systemic toxicity of LA (accidental intravenous)</td>
<td>Transient paresthesias, Spinal cord trauma, infection</td>
</tr>
<tr>
<td></td>
<td>Catheter complications (shearing, kinking, vascular or subarachnoid placement)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infection, Dural puncture</td>
<td></td>
</tr>
</tbody>
</table>

Combined Spinal-Epidural

Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter

Contraindications to Spinal/Epidural Anesthesia

- absolute contraindications
  - lack of trained personnel
  - lack of resuscitative drugs/equipment
  - patient refusal
  - allergy to local anesthetic
  - infection at puncture site or underlying tissues
  - coagulopathies/bleeding diathesis
  - raised ICP
  - sepsis/bacteremia
  - severe hypovolemia
  - cardiac lesion with fixed output states (e.g. severe mitral/aortic stenosis)
  - lack of IV access
- relative contraindications
  - pre-existing neurological disease (demyelinating lesions)
  - previous spinal injection, severe spinal deformity
  - prolonged surgery
  - major blood loss or maneuvers that can compromise reaction

Peripheral Nerve Blocks

- deposition of LA around the target nerve or plexus
- ultrasound guidance and peripheral nerve stimulation (needle will stimulate target nerve/plexus) may be used to guide needle to target nerve while avoiding neural trauma or intraneural injection
- approximately 2-4 per 10,000 risk of late neurologic injury
- most major nerves or nerve plexi can be targeted (e.g. brachial plexus block, femoral nerve block, sciatic nerve block, etc.)
- performed with standard monitors
- resuscitation equipment must be available

Contraindications to Peripheral Nerve Blockade

- absolute contraindications
  - allergy to LA
  - patient refusal
- relative contraindications
  - certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
  - local infection at block site
  - bleeding disorder

Classic Presentation of Dural Puncture Headache

- Onset 6 h-3 d after dural puncture
- Postural component (worse sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia

Reduction of Post-Operative Mortality and Morbidity with Epidural or Spinal Anaesthesia: Results from Overview of Randomized Trials

BMJ 2000;321:1-12

Purpose: To obtain reliable estimates of the effects of neuraxial blockade with epidural or spinal anaesthesia on post-operative morbidity and mortality after various surgeries with or without general anesthesia.

Study: Systematic review of all trials with randomization to intraoperative neuraxial blockade vs. control group.

Patients: 141 trials including 9,559 patients.

Main Outcomes: All cause mortality, MI, PE, DVT, transfusion requirements, pneumonia, other infections, respiratory depression, and renal failure.

Results: With neuraxial blockade, overall mortality was reduced by about one third. Neuraxial blockade reduced the risk of PE by 55%, DVT by 44%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59%. There were also reductions in MI and renal failure. These mortality reductions are irrespective of surgical group, type of blockade (epidural or spinal), or whether neuraxial blocker was combined with general anesthetic.

Conclusions: Neuraxial blockade reduces post-operative mortality, and other serious complications.
Local Anesthesia

Local Anesthetic Agents

- see Table 18, A30 for list of LA agents

Definition and Mode of Action
- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptors on the cytosolic side of the Na⁺ channel, inhibiting Na⁺ flux and thus blocking impulse conduction
- different types of nerve fibers undergo blockade at different rates

Absorption, Distribution, Metabolism
- LA readily crosses the blood-brain barrier (BBB) once absorbed into the bloodstream
- ester-type LA (procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- amide-type LA (lidocaine, bupivicaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

Selection of LA
- choice of LA depends on
  - onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA, and the faster the onset of action)
  - duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  - potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  - unique needs (e.g. sensory blockade with relative preservation of motor function by bupivicaine at low doses)
  - potential for toxicity

Systemic Toxicity
- see Table 18, A30 for maximum doses, potency, and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption
- CNS effects
  - CNS effects first appear to be excitatory due to initial block of inhibitory fibers, then subsequent block of excitatory fibers
  - effects in order of appearance
    - numbness of tongue, perioral tingling, metallic taste
    - disorientation, drowsiness
    - tinnitus
    - visual disturbances
    - muscle twitching, tremors
    - unconsciousness
    - convulsions, seizures
    - generalized CNS depression, coma, respiratory arrest
- CVS effects
  - vasodilation, hypotension
  - decreased myocardial contractility
  - dose-dependent delay in cardiac impulse transmission
    - prolonged PR, QRS intervals
    - sinus bradycardia
  - CVS collapse
- treatment of systemic toxicity
  - early recognition of signs, get help
  - 100% O₂, manage ABCs
  - diazepam or sodium thiopental may be used to increase seizure threshold
  - manage arrhythmias (see ACLS Guidelines, A32)
  - Intralipid 20% to bind local anesthesic in circulation

Figure 10. Local anesthetic systemic toxicity
Local Infiltration and Hematoma Blocks

Local Infiltration
- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerves
- suitable for small incisions, suturing, excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100,000-1:200,000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

Fracture Hematoma Block
- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

Topical Anesthetics
- various preparations of local anesthetics available for topical use, may be a mixture of agents (EMLA cream is a combination of 2.5% lidocaine and prilocaine)
- must be able to penetrate the skin or mucous membrane

Post-Operative Care
- pain management should be continuous from OR to post-anesthetic care unit (PACU) to hospital ward and home

Common Post-Operative Anesthetic Complications

Nausea and Vomiting
- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), metoclopramide (Maxeran®; not with bowel obstruction), prochlorperazine (Stemetil®), ondansetron (Zofran®), granisetron (Kytril®)

Confusion and Agitation
- ABCs first – confusion or agitation can be caused by airway obstruction, hypercapnea, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- pain, distended bowel/bladder
- fear/anxiety/separation from caregivers, language barriers
- metabolic disturbance (hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- intracranial cause (stroke, raised intracranial pressure)
- drug effect (ketamine, anticholinergics)
- elderly patients are more susceptible to post-operative delirium

Respiratory Complications
- susceptible to aspiration of gastric contents due to PONV and unreliable airway reflexes
- airway obstruction (secondary to reduced muscle tone from residual anesthetic, soft tissue trauma and edema, or pooled secretions) may lead to inadequate ventilation, hypoxemia, and hypercapnia
- airway obstruction can often be relieved with head tilt, jaw elevation, and anterior displacement of the mandible. If the obstruction is not reversible, a nasal or oral airway may be used

Hypotension
- must be identified and treated quickly to prevent inadequate perfusion and ischemic damage
- reduced cardiac output (hypovolemia, most common cause) and/or peripheral vasodilation (residual anesthetic agent)
- first step in treatment is usually the administration of fluids ± inotropic agents

Hypertension
- pain, hypercapnia, hypoxemia, increased intravascular fluid volume, and sympathomimetic drugs can cause HTN
- sodium nitroprusside or beta-blocking drugs (e.g. esmolol and metoprolol) can be used to treat HTN

Risk Factors for Post-Operative Nausea and Vomiting (PONV)
- Young age
- Female
- History of PONV
- Non-smoker
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: N2O, opioids, volatile agents

Drugs for Preventing Post-Operative Nausea and Vomiting
Cochrane DB Syst Rev 2006;3:CD004125
Purpose: To evaluate the efficacy of antiemetics in preventing PONV.
Methods: A meta-analysis was performed looking at randomized controlled trials comparing an antiemetic to either a second antiemetic or placebo. Trials looking at dosing and/or timing of medication administration were also included. PONV was used as the primary outcome.
Results: 737 studies involving 103,237 patients. Eight drugs significantly reduced the occurrence of PONV, namely: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine, and granisetron. Relative risk (RR) vs. placebo varied between 0.60-0.80. Side effects included a significant increase in drowsiness for droperidol (RR 1.32) and headache for ondansetron (RR 1.16). The cumulative number needed to treat was 3.57.
Conclusion: Antiemetic medication is effective for reducing the occurrence of PONV. However, further investigation needs to be done to determine whether antiemetics can cause more severe (and likely rare) side effects, which could alter how liberally they are used.
**Pain Management**

**Definitions**
- pain: perception of nociception, which occurs in the brain
- nociception: detection, transduction, and transmission of noxious stimuli

**Pain Classifications**
- temporal: acute vs. chronic
- mechanism: nociceptive vs. neuropathic

**Acute Pain**
- pain of short duration (<6 wk) usually associated with surgery, trauma, or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

---

**Pharmacological Management of Acute Pain**
- ask the patient to rate the pain out of 10, or use visual analog scale, to determine severity
- pharmacological treatment guided by WHO analgesia ladder
- patient controlled analgesia (PCA)
  - involves the use of computerized pumps that can deliver a constant infusion as well as bolus breakthrough doses of parenterally-administered opioid analgesics
  - limited by lockout intervals
  - most commonly used agents: morphine and hydromorphone
- see Table 13, A28 for suggested infusion rate, PCA dose and lockout intervals

**Table 10. Commonly Used Analgesics**

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tylenol®</td>
<td>Aspirin® + ibuprofen, naproxen ketorolac (IV)</td>
<td>Oral: codeine, oxycodone, morphine, hydromorphone Parenteral: morphine, hydromorphone, fentanyl</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-line for mild acute pain</td>
<td>Mild-moderate pain</td>
<td>Oral: moderate acute pain Parenteral: moderate-severe acute pain</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unclear, hypothesized cyclooxygenase-2 (COX-2) inhibition</td>
<td>Non-selective COX-1 and 2 inhibition reducing proinflammatory prostaglandin synthesis</td>
<td>Dampens nociceptive transmission between 1st and 2nd order neurons in the dorsal horn Activates ascending modulatory pathways resulting in release of inhibitory neurotransmitters Inhibits peripheral inflammatory response and hyperalgesia Affects mood and anxiety – alleviates the affective component of perceived pain</td>
</tr>
</tbody>
</table>

---

**Figure 11. Acute pain mechanism**

**Figure 12. WHO analgesia ladder**

**Opioid Conversion**

<table>
<thead>
<tr>
<th>Parenteral (IV)</th>
<th>Equivalent Oral Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>120 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>100 mcg</td>
</tr>
<tr>
<td>Fentanyl IV</td>
<td>N/A</td>
</tr>
</tbody>
</table>

---

**Cautionary Use of NSAIDs in Patients with:**
- Asthma
- Coagulopathy
- GI ulcers
- Renal insufficiency
- Pregnancy, 3rd trimester

**Common Side Effects of Opioids**
- N/V
- Constipation
- Sedation
- Pruritus
- Abdominal pain
- Urinary retention
- Respiratory depression

When prescribing opioids, consider:
- Breakthrough dose
- Anti-emetics
- Laxative

**PCA Parameters**
- Loading dose
- Bolus dose
- Lockout interval
- Continuous infusion (optional)
- Maximum 4 h dose (limit)

**Advantages of PCA**
- Improved patient satisfaction
- Fewer side effects
- Accommodates patient variability
- Accommodates changes in opioid requirements
Physiologic Changes in Pregnancy

- Airway
  - possible difficult airway as tissues becomes edematous and friable especially in labor
- Respiratory
  - decreased FRC and increased O₂ consumption → desaturation occurs more quickly during anesthesia
- Cardiovascular system
  - increased blood volume > increased RBC mass → mild anemia
  - decreased SVR proportionately greater than increased CO → decreased BP
  - prone to decreased BP due to aortocaval compression – therefore for surgery, a pregnant patient is positioned in left uterine displacement using a wedge under her right flank
- Central nervous system
  - decreased MAC due to hormonal effects
  - increased block height due to engorged epidural veins
- Gastrointestinal system
  - delayed gastric emptying
  - increased volume and acidity of gastric fluid
  - decreased LES tone
  - increased abdominal pressure
  - combined, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity

Opioid Antagonists (naloxone, naltrexone)

- indication: opioid overdose (manifests primarily at CNS, e.g. respiratory depression)
- mechanism of action: competitively inhibit opioid receptors, predominantly µ receptors
  - naloxone is short-acting (t½ = 1 h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
  - naltrexone is longer-acting (t½ = 10 h); less likely to see return of opioid effects
- Side Effects/Toxicity
  - Gastric ulceration/bleeding
  - Decreased renal perfusion
  - Photosensitivity
  - Premature closure of the ductus arteriosus in pregnancy
  - Respiratory depression
  - Constipation and abdominal pain
  - Sedation
  - N/V
  - Pruritus
  - Confusion (particularly in the elderly)
  - Dependence

Neuropathic Pain

- pain caused by peripheral or central nervous system injury, often described as burning, lancinating, shooting, or tingling
- results in allodynia (pain in response to normally painless stimuli) or hyperalgesia (increased sensitivity to painful stimuli)
- consider adding anticonvulsants (gabapentin, pregabalin) or low-dose tricyclic antidepressant as opioids are ineffective

Chronic Pain

- chronic pain: greater than 3 mo, or recurrent pain that occurs at least 3 times throughout three month period
- pain of duration or intensity that persists beyond normal tissue healing and adversely affects functioning
- may have nociceptive and neuropathic components; dysregulation of analgesic pathways implicated
- in the perioperative period, consider continuing regular long-acting analgesics and augmenting with regional techniques, adjuvants, additional opioid analgesia, and non-pharmacological techniques

Obstetrical Anesthesia

Patient Controlled Opioid Analgesia vs. Conventional Opioid Analgesia for Post-Operative Pain

Cochrane Database Syst Rev 2006;4:CD003348

Purpose: To evaluate the efficacy of patient controlled analgesia (PCA) as compared to conventional as-needed analgesia administration providing pain relief in post-operative patients.

Methods: Meta-analyses of randomized controlled trials comparing PCA vs. conventional administration of opioid analgesia. Assessment employed a visual analog scale (VAS) for pain intensity along with overall analgesic consumption, patient satisfaction, length of stay, and adverse side effects.

Results: 55 studies with a total of 2,023 patients receiving PCA and 1,838 patients with standard as-needed opioid administration. PCA provided significantly better pain control through 72 h post-operatively, but patients consumed significantly more opioids (> 7 mg morphine/24 h, p < 0.05). Significantly more patients reported pruritus in the PCA group compared to controls with a number needed to harm of 13. No significant difference in overall length of stay in hospital, sedation level, N/V, or urinary retention.

Conclusions: PCA is more effective than standard as-needed administration for reducing post-operative pain. However, patients using PCA consume more opioids overall, and have more pruritus.

Table 10. Commonly Used Analgesics (continued)

<table>
<thead>
<tr>
<th>Dosing/Administration</th>
<th>Acetaminophen</th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited by analgesic ceiling beyond which there is no additional analgesia</td>
<td>Limited by analgesic ceiling beyond which there is no additional analgesia</td>
<td>No analgesic ceiling (except for codeine)</td>
<td></td>
</tr>
<tr>
<td>Opioid-sparing</td>
<td>Opioid-sparing</td>
<td>Can be administered intrathecally (spinal block) or by continuous infusion</td>
<td></td>
</tr>
<tr>
<td>Max dose of 4 g/24 h</td>
<td>Significant inter-individual variation in efficacy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effects/Toxicity</th>
<th>Gastric ulceration/bleeding</th>
<th>Decreased renal perfusion</th>
<th>Photosensitivity</th>
<th>Premature closure of the ductus arteriosus in pregnancy</th>
<th>Respiratory depression</th>
<th>Constipation and abdominal pain</th>
<th>Sedation</th>
<th>N/V</th>
<th>Pruritus</th>
<th>Confusion (particularly in the elderly)</th>
<th>Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considered relatively safe</td>
<td>Increased block height due to engorged epidural veins</td>
<td>Increased abdominal pressure</td>
<td>Combined, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver toxicity in elevated doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The Effect of Epidural Analgesia on Labor, Maternal, and Neonatal Outcomes: A Systematic Review

Am J Obstet Gynecol 2002;186:S69-77

Study: Meta-analysis of 14 studies with 4,324 women.

Selection Criteria: RCTs and prospective cohort studies between 1980-2001 comparing epidural analgesia to parenteral opioid administration during labor.

Types of Participants: Healthy women with uneventful pregnancies.

Intervention: Participants were randomized to either epidural analgesia or parenteral opioid administration during labor.

Outcomes and Results: Maternal – there were no differences between the 2 groups in first-stage labor length, incidence of Cesarean delivery, incidence of instrumented vaginal delivery for dystocia, nausea, or mid-to-low back pain post-partum. However, second-stage labor length was longer (mean=15 min) and there were greater reports of lower and hypertension in the epidural group. Also, lower pain scores and greater satisfaction with analgesia were reported among the epidural group. There was no difference in lactation success at 6 wk and urinary incontinence was more frequent in the epidural group immediately post-partum, but not at 3 mo or 1 yr (evidence from PC studies only).

Neonatal – there were no differences between the 2 groups for incidence of fetal heart rate abnormalities, intrapartum meconium, poor 5-min Apgar score, or low umbilical artery pH. However, the incidence of poor 1-min Apgar scores and need for neonatal naloxone were higher in the parenteral opioid group.

Conclusions: Epidural analgesia is a safe intrapartum method for labor pain relief and women should not avoid epidural analgesia for fear of neonatal harm. Cesarean delivery, breastfeeding difficulties, long-term back pain, or long-term urinary incontinence.
Options for Analgesia during Labor

• Psychoprophylaxis – Lamaze method
  ▪ patterns of breathing and focused attention on fixed object
• Systemic medication
  ▪ easy to administer, but risk of maternal or neonatal depression
  ▪ opioids most commonly used if delivery is not expected within 4 h
• Inhalational analgesia
  ▪ easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
  ▪ 50% nitrous oxide
• Neuraxial anesthesia
  ▪ provides excellent analgesia with minimal depressant effects
  ▪ hypotension is the most common complication
  ▪ maternal BP monitored q2-5 min for 15-20 min after initiation and regularly thereafter
  ▪ epidural usually given as it preferentially blocks sensation, leaving motor function intact

Options for Caesarean Section

• neuraxial: spinal or epidural
• general: used if contraindications or time precludes regional blockade

Pediatric Anesthesia

Respiratory System

• in comparison to adults, anatomical differences in infants include:
  ▪ large head, short trachea/neck, large tongue, adenoids, and tonsils
  ▪ narrow nasal passages (obligate nasal breathers until 5 mo)
  ▪ narrowest part of airway at the level of the cricoid vs. glottis in adults
  ▪ epiglottis is longer, U shaped and angled at 45 degrees; carina is wider and is at the level of T2 (T4 in adults)
• physiologic differences include
  ▪ faster RR, immature respiratory centers which are depressed by hypoxia/hypercapnea
  ▪ less oxygen reserve during apnea – decreased total lung volume, vital and functional reserve capacity together with higher metabolic needs
• greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  ▪ greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm, and higher resistance to airflow

Cardiovascular System

• blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume lost
• children have a high HR and low BP
• CO is dependent on HR, not stroke volume because of low heart wall compliance; therefore, bradycardia → severe compromise in CO

Temperature Regulation

• vulnerable to hypothermia
• minimize heat loss by use of warming blankets, covering the infant's head, humidification of inspired gases, and warming of infused solutions

Central Nervous System

• MAC of halothane is increased compared to the adult (0.75% adult, 1.2% infant, 0.87% neonate)
• NMJ is immature for the first 4 wk of life and thus there is an increased sensitivity to non-depolarizing relaxants
• parasympathetics mature at birth, sympathetics mature at 4-6 mo → autonomic imbalance
• infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

Glucose Maintenance

• infants less than 1 yr old can become seriously hypoglycemic during pre-operative fasting and post-operatively if feeding is not recommenced as soon as possible
• after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

Pharmacology

• higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
• barbiturates/opioids more potent due to greater permeability of BBB
• muscle relaxants

To increase alveolar minute ventilation in neonates, increase respiratory rate, not tidal volume.

Neonate: 30-40 breaths/min
Age 1-13: (24 – [age/2]) breaths/min
Uncommon Complications

Malignant Hyperthermia

- hypermetabolic disorder of skeletal muscle due to an uncontrolled increase in intracellular Ca\(^{2+}\)
- pathogenesis: Genetic anomaly (autosomal dominant) of ryanodine receptor which regulates the Ca\(^{2+}\) channel in the sarcoplasmic reticulum of skeletal muscle
- incidence of 1-5 per 100,000; may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH include:
  - all inhalational agents except nitrous oxide
  - depolarizing muscle relaxant – SCh

Clinical Picture
- onset: immediate or hours after contact with trigger agent
  - increased oxygen consumption
  - increased ETCO\(_2\) on capnograph
  - tachycardia/dysrhythmia
  - tachypnea/cyanosis
  - diaphoresis
  - HTN
  - increased temperature (late sign)
- muscular symptoms
  - trismus (masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  - tender, swollen muscles due to rhabdomyolysis
  - trunk or total body rigidity

Complications
- coma
- DIC
- rhabdomyolysis
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema
- can be fatal if untreated

Prevention
- suspect MH in patients with a family history of problems/death with anesthetic
- avoid all trigger medications, use vapour free equipment, use regional anesthesia if possible
- central body temp and ET\(_{CO_2}\) monitoring

Malignant Hyperthermia Management (Based on Malignant Hyperthermia Association of the U.S. [MHAUS] Guidelines, 2008)
1. notify surgeon, discontinue volatile agents and succinylcholine, hyperventilate with 100% oxygen at flows of 10 L/min or more, halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
3. repeat until there is control of signs of MH; sometimes up to 30 mg/kg is necessary
4. cool patients with core temperature >39°C
  - lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
  - stop cooling if temperature is <38°C to prevent drift to <36°C
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
  - use standard drug therapy except Ca\(^{2+}\) channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene

ETT Sizing in Pediatrics
Diameter (mm) of tracheal tube in children after 1 year = (age/4) + 4
Length (cm) of tracheal tube = (age/2) + 12

Signs of Malignant Hyperthermia
- Unexplained rise in ETCO\(_2\)
- Increase in minute ventilation
- Tachycardia
- Rigidity
- Hyperthermia (late sign)

Basic Principles of MH Management
“Some Hot Dude Better Get Iced Fluids Fast”
Stop all triggering agents, give 100% O\(_2\)
Hyperventilate
Dantrolene 2.5 mg/kg every 5 min
Bicarbonate
Glucose and insulin
IV fluids; cool patient to 38°C
Fluid output; consider furosemide
Tachycardia: be prepared to treat VT
6. hyperkalemia
   ▪ treat with hyperventilation, bicarbonate, glucose/insulin, calcium
   ▪ bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg
   for life-threatening hyperkalemia and check glucose levels hourly
7. follow ETCO2, electrolytes, blood gases, creatine kinase (CK), core temperature, urine output/color with Foley catheter, coagulation studies
   ▪ if CK and/or potassium rises persistently or urine output falls to <0.5 mL/kg/h, induce diuresis to >1 mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids, and propofol
9. transfer to ICU bed

Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- individuals with abnormal pseudocholinesterase will have prolonged muscular blockade
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors)

Common Medications

Table 11. Intravenous Induction Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Action</th>
<th>Indication</th>
<th>Caution</th>
<th>Dosing</th>
<th>Additional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol (Diprivan®)</td>
<td>Alkylphenol – hypnotic</td>
<td>Ultra-short acting thiobarbiturate – hypnotic</td>
<td>Induction</td>
<td>Induction</td>
<td>IV induction: 2.5-3.0 mg/kg (less with opioids)</td>
<td>0-30% decreased BP due to vasodilation Reduce burning at IV site by mixing with lidocaine</td>
</tr>
<tr>
<td>Thiopental (sodium thiopentone)</td>
<td>Ultra-short acting thiobarbiturate – hypnotic</td>
<td>Decreased time Cl– channels open, facilitating GABA and suppressing glutamic acid</td>
<td>Control of convulsive states</td>
<td>Unconscious &lt;1 min</td>
<td>IV induction: 3-5 mg/kg</td>
<td>Combining with rocuronium causes precipitates to form</td>
</tr>
<tr>
<td>Ketamine (Ketalar®, Ketaject®)</td>
<td>Phencyclidine (PCP) derivative – dissociative</td>
<td>May act on NMDA, opiates, and other receptors</td>
<td>Major trauma, hypovolemia, severe asthma because sympathomimetic</td>
<td>Allergy (egg, soy) Patients who cannot tolerate sudden decreased BP (e.g. fixed cardiac output or shock)</td>
<td>IV induction 1-2 mg/kg</td>
<td>High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions)</td>
</tr>
<tr>
<td>Benzodiazepines (midazolam (Versed®), diazepam (Valium®), lorazepam (Ativan®))</td>
<td>Causes increased glycine inhibitory neurotransmitter, facilitates GABA</td>
<td>Causes increased glycine inhibitory neurotransmitter, facilitates GABA</td>
<td>Ketamine allergy</td>
<td>Allergy to barbiturates Uncontrolled hypotension, shock, cardiac failure</td>
<td>Dissociation in 15 s, analgesia, amnesia, and unconsciousness in 45-60 s</td>
<td>Antagonist: flumazenil (Romazicon®) competitive inhibitor, 0.2 mg IV over 15 s, repeat with 0.1 mg/min (max of 2 mg), t1/2 = 60 min</td>
</tr>
</tbody>
</table>

Additional Notes:
- 0-30% decreased BP due to vasodilation
- Reduce burning at IV site by mixing with lidocaine
### Table 12. Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Dose to 10 mg Morphine IV</th>
<th>Moderate Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>200 mg PO</td>
<td>15-30 mg PO</td>
<td>Late (30-60 min)</td>
<td>Moderate (4-6 h)</td>
<td>Primarily post-operative use, not for IV use</td>
</tr>
<tr>
<td>Meperidine (Demerol&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>75 mg IV</td>
<td>2-3 mg/kg IV</td>
<td>Moderate (10 min)</td>
<td>Moderate (2-4 h)</td>
<td>Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg IV</td>
<td>0.2-0.3 mg/kg IV</td>
<td>Moderate (5-10 min)</td>
<td>Moderate (4-5 h)</td>
<td>Histamine release leading to decrease in BP</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>15 mg PO</td>
<td>10-20 mg PO (no IV)</td>
<td>Late (30-45 min)</td>
<td>Long (8-12 h)</td>
<td>Do not split, crush, or chew tablet</td>
</tr>
<tr>
<td>Oxycodone Controlled Release</td>
<td>15 mg PO (no IV)</td>
<td>5-15 mg PO</td>
<td>Moderate (15 min)</td>
<td>Moderate (3-6 h)</td>
<td>Percocet&lt;sup&gt;®&lt;/sup&gt; = oxycodone 5 mg + acetaminophen 325 mg</td>
</tr>
<tr>
<td>Hydromorphone (Dilaudid&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>2 mg IV</td>
<td>40-60 µg/kg IV</td>
<td>Moderate (15 min)</td>
<td>Moderate (4-5 h)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100 µg IV</td>
<td>2-3 µg/kg IV</td>
<td>Rapid (&lt;5 min)</td>
<td>Short (0.5-1 h)</td>
<td>Transient muscle rigidity in very high doses</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>100 µg IV</td>
<td>0.5-1.5 µg/kg IV</td>
<td>Rapid (1-3 min)</td>
<td>Ultra short (&lt;10 min)</td>
<td>Only use during induction and maintenance of anesthesia</td>
</tr>
</tbody>
</table>

In general, parenteral route is 2-3x more potent than oral.

### Table 13. Opioid PCA Doses

<table>
<thead>
<tr>
<th>Agent</th>
<th>PCA Dose</th>
<th>PCA Lockout Interval</th>
<th>PCA 4 h Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1 mg</td>
<td>5 min</td>
<td>30 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25-50 µg</td>
<td>5 min</td>
<td>400 µg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.2 mg</td>
<td>5 min</td>
<td>6 mg</td>
</tr>
</tbody>
</table>

### Table 14. Volatile Inhalational Agents

<table>
<thead>
<tr>
<th>Sevoflurane</th>
<th>Desflurane</th>
<th>Isoflurane</th>
<th>Enflurane</th>
<th>Halothane</th>
<th>Nitrous oxide (N&lt;sub&gt;2&lt;/sub&gt;O)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>6.0</td>
<td>1.2</td>
<td>1.7</td>
<td>0.8</td>
<td>104</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MAC (% gas in O&lt;sub&gt;2&lt;/sub&gt;)</th>
<th>CNS</th>
<th>Resp</th>
<th>CVS</th>
<th>MSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0</td>
<td>Increased ICP</td>
<td>Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory CO&lt;sub&gt;2&lt;/sub&gt; reflexes, bronchodilation</td>
<td>Less decrease of contractility, stable HR</td>
<td>Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation</td>
</tr>
<tr>
<td>6.0</td>
<td>Increased ICP</td>
<td></td>
<td>Tachycardia with rapid increase in concentration</td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>Decreased cerebral metabolic rate</td>
<td></td>
<td>Decreased BP and CO, increased HR, theoretical chance of coronary steal**</td>
<td></td>
</tr>
<tr>
<td>1.7</td>
<td>Increased ICP</td>
<td></td>
<td>Stable HR, decreased contractility</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td>Increased ICP</td>
<td></td>
<td>Decreased BP, CO, HR, and conduction sensitizes myocardium to epinephrine-induced arrhythmias</td>
<td></td>
</tr>
<tr>
<td>104</td>
<td>Increased ICP</td>
<td></td>
<td>Can cause decreased HR in pediatric cases in those with existing heart disease</td>
<td></td>
</tr>
</tbody>
</table>

**Coronary steal: sevoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion (e.g. stents, atherosclerosis)**
### Table 15. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)

**Mechanism of Action**
Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh.

**Intubating Dose**
1-1.5 mg/kg

**Onset**
30-60 s – RAPID (fastest of all muscle relaxants)

**Duration**
3-5 min – SHORT (no reversing agent for SCh)

**Metabolism**
SCh is hydrolyzed by plasma cholinesterase (pseudocholinesterase), found only in plasma and not at the NMJ.

**Indications**
- Assist intubation
- Increased risk of aspiration (need rapid paralysis and airway control)
- Short procedures (e.g. full stomach), hiatus hernia, obesity, pregnancy, trauma
- Electroconvulsive therapy (ECT)
- Laryngospasm

**Side Effects**
1. SCh also stimulates muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors)
   - May cause bradycardia, dysrythmias, sinus arrest, increased secretions of salivary glands (especially in children)
2. Hyperkalemia
   - Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors
   - Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells
   - Patients at risk:
     - 3rd degree burns 24 h-6 mo after injury
     - Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy)
     - Severe intra-abdominal infections
     - Severe closed head injury
     - Upper motor neuron lesions
3. Can trigger MH
4. Increased ICP/intraocular pressure/intragastric pressure (no increased risk of aspiration if competent lower esophageal sphincter)
5. Fasciculations, post-operative myalgia – may be minimized if small dose of non-depolarizing agent given before SCh administration

**Contraindications**

| Absolute | Known hypersensitivity or allergy, positive history of malignant hyperthermia, myotonia (m. congenita, m. dystrophica, paramyotonia congenital), high risk for hyperkalemia response |
| Relative | Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury |

### Table 16. Non-Depolarizing Muscle Relaxants (Competitive)

**Mechanism of Action**
Competitive blockade of postsynaptic ACh receptors preventing depolarization.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Short</th>
<th>Intermediate</th>
<th>Long</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mivacurium</td>
<td>0.2</td>
<td>0.6-1.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>2-3</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>15-25</td>
<td>30-45</td>
<td>45-60</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td></td>
<td>40-60</td>
<td>90-120</td>
</tr>
<tr>
<td>Pancuronium</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Metabolism**
Plasma cholinesterase
Liver (major)
Liver (minor)
Hofmann Eliminations
Liver (major)
Liver (minor)

**Indications**
Assist intubation, assist mechanical ventilation in some ICU patients, reduce fasciculations and post-operative myalgias secondary to SCh.

**Side Effects:**

<table>
<thead>
<tr>
<th>Histamine Release</th>
<th>Yes</th>
<th>No</th>
<th>No</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td>Tachycardia</td>
</tr>
</tbody>
</table>

**Considerations**

<table>
<thead>
<tr>
<th>Increased duration of action in renal or liver failure</th>
<th>Quick onset of rocuronium allows its use in rapid sequence induction</th>
<th>Cisatracurium is good for patients with renal or hepatic insufficiency</th>
<th>Pancuronium if increased HR and BP desired</th>
</tr>
</thead>
</table>
Table 17. Reversal Agents for Non-Depolarizing Relaxants

<table>
<thead>
<tr>
<th>Cholinesterase Inhibitor</th>
<th>Neostigmine</th>
<th>Pyridostigmine</th>
<th>Edrophonium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset and Duration</td>
<td>Intermediate</td>
<td>Longest</td>
<td>Shortest</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Inhibits enzymatic degradation of ACh, increases ACh at nicotinic and muscarinic receptors, displaces non-depolarizing muscle relaxants</td>
<td>Muscarinic effects of reversing agents include unwanted bradycardia, salivation, and increased bowel peristalsis*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose</th>
<th>0.04-0.08 mg/kg</th>
<th>0.1-0.4 mg/kg</th>
<th>0.5-1 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of Anticholinergic per mg</td>
<td>0.2 mg</td>
<td>0.05 mg</td>
<td>0.014 mg</td>
</tr>
</tbody>
</table>

*Atropine and glycopyrrolate are anticholinergic agents administered during the administration of reversal agents to minimize muscarinic effects

Table 18. Local Anesthetic Agents

<table>
<thead>
<tr>
<th>Local Anesthetic Agent</th>
<th>Chloroprocaine</th>
<th>Lidocaine</th>
<th>Bupivacaine</th>
<th>Ropivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum Dose (mg/kg)</td>
<td>11</td>
<td>5</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Maximum Dose with Epinephrine (mg/kg)</td>
<td>14</td>
<td>7</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Potency</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Duration (min/h)</td>
<td>15-30</td>
<td>1-2</td>
<td>3-8</td>
<td>2-8</td>
</tr>
</tbody>
</table>

Appendices

Difficult Tracheal Intubation in Unconscious Patient

Figure 14. Difficult tracheal intubation encountered in the unconscious patient

SGD = supraglottic device

Difficult Tracheal Intubation

Figure 15. Anticipated difficult tracheal intubation
SGD = supraglottic device

Advanced Cardiac Life Support (ACLS) Guidelines

Figure 16. Adult cardiac arrest algorithm
**Adult Tachycardia (With Pulse)**

1. **Assess appropriateness for clinical condition**
   Heart rate typically ≥150/min if tachyarrhythmia

2. **Identify and treat underlying cause**
   - Maintain patent airway; assist breathing as necessary
   - Oxygen (if hypoxemic)
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry

3. **Persistent tachyarrhythmia causing:**
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. **Synchronized cardioversion**
   - Consider sedation
   - If regular narrow complex, consider adenosine

5. **Wide QRS? ≥0.12 second**
   - No
   - IV access and 12-lead ECG if available
   - Vagal maneuvers
   - Adenosine (if regular)
   - β-Blockers or calcium channel blocker
   - Consider expert consultation

6. **Monitor and observe**
   - Yes
   - IV access and 12-lead ECG if available
   - Consider adenosine only if regular and monomorphic
   - Consider antiarrhythmic infusion
   - Consider expert consultation

**Doses/Details**

**Synchronized Cardioversion**
- Initial recommended doses:
  - Narrow regular: 50-100 J
  - Narrow irregular: 120-200 J monophasic
  - Wide regular: 100 J
  - Wide irregular: defibrillation dose (NOT synchronized)

**Adenosine IV Dose:**
- First dose: 6 mg rapid IV push; follow with NS flush
- Second dose: 12 mg if required

**Antiarrhythmic Infusions for Stable Wide-QRS Tachycardia**
- **Procainamide IV Dose:**
  - 20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases ≥50%, or maximum dose 17 mg/kg given
  - Maintenance infusion: 1-4 mg/min
  - Avoid if prolonged QT or CHF

- **Sotalol IV Dose:**
  - 100 mg (1.5 mg/kg) over 5 min
  - Avoid if prolonged QT

**Figure 17. Adult tachycardia algorithm**

---

**Adult Bradycardia (With Pulse)**

1. **Assess appropriateness for clinical condition**
   Heart rate typically <50/min if bradyarrhythmia

2. **Identify and treat underlying cause**
   - Maintain patent airway; assist breathing as necessary
   - Oxygen (if hypoxemic)
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
   - IV access
   - 12-Lead ECG if available; do not delay therapy

3. **Persistent bradyarrhythmia causing:**
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. **Monitor and observe**
   - No

5. **Atropine**
   - If atropine ineffective:
     - Transcutaneous pacing OR
     - Dopamine infusion OR
     - Epinephrine infusion

6. **Consider:**
   - Expert consultation
   - Transvenous pacing

**Doses/Details**

**Atropine IV Dose:**
- First dose: 0.5 mg bolus
- Repeat every 3-5 min
- Max: 3 mg

**Dopamine IV Infusion:**
- 2-10 µg/kg/min

**Epinephrine IV Infusion:**
- 2-10 µg/min

**Figure 18. Adult bradycardia algorithm**
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Acronyms

AAA abdominal aortic aneurysm
ABI ankle-brachial index
ACEI angiotensin converting enzyme inhibitor
ACS acute coronary syndrome
AFib atrial fibrillation
AR aortic regurgitation
ARB angiotensin receptor blocker
ARDS acute respiratory distress syndrome
AS aortic stenosis
ASA acetylsalicylic acid (Aspirin®)
AV atrioventricular
AVM arteriovenous malformation
AVRT atrioventricular re-entrant tachycardia
BBB bundle branch block
BNP brain natriuretic peptide
BP blood pressure
CABG coronary artery bypass graft
CAD coronary artery disease
CCB calcium channel blocker
CHF congestive heart failure
CI cardiac index
CO cardiac output
COPD chronic obstructive pulmonary disease
CTA CT angiography
cvd carotid disease

Basic Anatomy Review

Coronary Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the root of the aorta
  - right coronary artery (RCA)
    - acute marginal branches
    - atrioventricular (AV) nodal artery
    - posterior interventricular artery (PIV) = posterior descending artery (PD)
  - left main coronary artery (LCA): two major branches
    - left anterior descending artery (LAD)
      - septal branches
      - diagonal branches
    - left circumflex artery (LC)
      - obtuse marginal branches
- dominance of circulation
  - right-dominant circulation: PIV and at least one posterolateral branch arise from RCA (80%)
  - left-dominant circulation: PIV and at least one posterolateral branch arise from LC (15%)
  - balanced circulation: dual supply of posteroinferior LV from RCA and LC (5%)
- the sinoatrial (SA) node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
- most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through thebesian veins into all four chambers, contributing to the physiologic R-L shunt

Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)
Cardiac Anatomy

- layers of the heart
  - endocardium
  - myocardium
  - epicardium
  - visceral pericardium
  - pericardial cavity
  - parietal pericardium

- valves
  - semilunar valves: no subvalvular apparatus present
    - aortic valve, 3 valve leaflets: separates LV and ascending aorta
    - pulmonic valve, 3 valve leaflets: separates RV and main pulmonary artery (PA)
  - atrioventricular valves: subvalvular apparatus present in the form of chordae tendinae and papillary muscles
    - tricuspid valve, 3 valve leaflets: separates RA and RV
    - mitral valve, 2 valve leaflets: separates LA and LV

- conduction system
  - SA node governs pacemaking control
  - anterior-, middle-, and posterior-internal nodal tracts carry impulses in the right atrium and along Bachmann's bundle in the left atrium
  - atrial impulses converge at the AV node
    - the AV node is the only conducting tract from the atria to the ventricles because of electrical isolation by the annulus fibrosis (except when accessory pathways are present)
  - the bundle of His bifurcates into left and right bundle branches (LBB and RBB)
  - LBB further splits into anterior and posterior fascicles
  - RBB and fascicles of LBB give off Purkinje fibers which conduct impulses into the ventricular myocardium

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Figure 2a. Cardiac cycle
They gray shaded bars indicate isovolumic contraction (left) and isovolumic relaxation (right).

Figure 2b. JVP waveform

Legend:
- AV – aortic valve
- LA – left atrium
- LV – left ventricle
- MV – mitral valve

Figure 3. Conduction system of the heart

Figure 4. Blood vessel structure

Features of Abnormal JVP Wave Formation
- Atrial fibrillation: absent a wave
- 3rd degree heart block: cannon a waves
- Tricuspid regurgitation: cv wave, elevated JVP
- Cardiac tamponade: x descent only, absent y descent
- Constrictive pericarditis: prominent y descent, Kussmaul's sign (paradoxical increase in JVP with inspiration)
cardiovascular innervation
  - sympathetic nerves
    - innervate the SA node, AV node, ventricular myocardium and vasculature
    - SA node (β1) fibers increase pacemaking activity (chronotropy)
    - cardiac muscle (β1) fibers increase contractility (inotropy) to help increase cardiac output
    - stimulation of β1- and β2-receptors in the skeletal and coronary circulation causes vasodilatation
  - parasympathetic nerves
    - innervate the SA node, AV node, atrial myocardium but few vascular beds
    - basal vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node resulting in slowing of pacemaker activity and conduction (i.e. reduced dromotropy – if only affecting AV node conduction)
    - parasympathetics have very little impact on total peripheral vascular resistance

Differential Diagnoses of Common Presentations

Chest Pain
- cardiac
  - MI/angina
  - myocarditis
  - pericarditis/Dressler’s syndrome
  - cardiac tamponade
- pulmonary
  - pneumonia
  - PE
  - pneumothorax/hemothorax, tension pneumothorax
  - empyema
  - pulmonary neoplasm
  - bronchiecstasy
  - TB
- gastrointestinal
  - esophageal: spasm, GERD, esophagitis, ulceration, achalasia, neoplasm, Mallory-Weiss syndrome, esophageal rupture
- gastrointestinal
  - PUD
  - gastritis
  - pancreatitis
  - biliary colic
  - mediastinal
    - lymphoma
    - thymoma
  - vascular
    - dissecting aortic aneurysm
    - aortic rupture
    - surface structures
      - costochondritis
      - rib fracture
      - skin (bruising, herpes zoster)
      - breast
    - anxiety/psychosomatic

Loss of Consciousness
- hypovolemia
- cardiac
  - structural or obstructive causes
    - ACS
    - AS
    - HCM
    - cardiac tamponade, constrictive pericarditis
    - arrhythmias (see Arrhythmias, C15)
- respiratory
  - massive pulmonary embolism
  - pulmonary HTN
  - hypoxia
  - hypercapnia
  - neurologic
  - stroke/TIA (esp. vertebrobasilar insufficiency)
  - migraine
  - seizure
  - metabolic
    - anemia
    - hypoglycemia
  - drugs
    - antihypertensives
    - antiarrhythmics
    - diuretics
  - vasovagal
    - autonomic dysfunction
    - diabetic neuropathy
    - psychiatric
    - panic attack

Local Edema
- inflammation/infection
- venous or lymphatic obstruction
  - thrombophlebitis/deep vein thrombosis
  - venous insufficiency
  - chronic lymphangitis
  - lymphatic tumor infiltration
  - filariasis

Generalized Edema
- increased hydrostatic pressure/fluid overload
  - heart failure
  - pregnancy
  - drugs (e.g. CCBs)
  - iatrogenic (e.g. IV fluids)
  - decreased oncotic pressure/hypoalbuminemia
  - nephrotic syndrome
- liver cirrhosis
- malnutrition
- increased capillary permeability
- severe sepsis
- hormonal
  - hypothyroidism
  - exogenous steroids
- pregnancy
- estrogens
Palpitations

- cardiac
  - arrhythmias (PAC, PVC, SVT, VT)
  - valvular heart disease
  - HCM
- endocrine
  - thyrotoxicosis
  - pheochromocytoma
  - hypoglycemia
- systemic
  - fever
  - anemia
- drugs
  - stimulants and anticholinergics
- psychiatric
  - panic attack

Dyspnea

- cardiovascular
  - acute MI
  - CHF/LV failure
  - aortic/mitral stenosis
  - aortic/mitral regurgitation
  - arrhythmia
  - cardiac tamponade
  - restrictive pericarditis
  - left-sided obstructive lesions (e.g. left atrial myxoma)
  - elevated pulmonary venous pressure
- respiratory
  - airway disease
    - asthma
  - COPD exacerbation
  - upper airway obstruction (anaphylaxis, foreign body, mucus plugging)
  - parenchymal lung disease
    - ARDS
  - pneumonitis
  - interstitial lung disease
  - pulmonary vascular disease
    - PE
  - pulmonary HTN
  - pulmonary vasculitis
  - pleural disease
    - pneumothorax
  - pleural effusion
  - neuromuscular and chest wall disorders
    - C-spine injury
  - polynysoitis, myasthenia gravis, Guillain-Barré syndrome
  - kyphoscoliosis
  - anxiety/psychosomatic
    - hemorrhagic/metabolic
      - anemia, acidosis, hypercapnia

Cardiac Diagnostic Tests

Electrocardiography Basics

- the electrocardiogram (ECG) is a graphic representation of the electrical activity of the heart recorded from the surface of the body
- on the ECG graph
  - the horizontal axis represents time (at usual paper speed 25 mm/s)
    - 1 mm (1 small square) = 40 msec
    - 5 mm (1 large square) = 200 msec
  - the vertical axis represents voltage (at usual standard gain setting)
    - 1 mm (1 small square) = 0.1 mV
    - 10 mm (2 large squares) = 1 mV
- leads
  - standard 12-lead ECG
    - limb leads: I, II, III, aVL, aVR, aVF
    - precordial leads: V1-V6 (V1-V2 septal, V3-V4 anterior, V5-V6 lateral)
  - additional leads
    - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
  - lateral = I, aVL, V5, V6; inferior = II, III, aVF; anterior = V1-V4

Approach to ECGs

Introduction
Historically, the electrocardiogram has been a tricky subject for medical students. For many years, the classical approach has been taught in medical schools, which has demystified the ECG. Below, we are presenting both the Classical Approach and the newer PQRSTU Approach to provide students with different ways to view the ECG. Despite methodological differences, the rigor and final result is the same. These two approaches should help you better understand the concepts of ECG interpretation and equip you with the necessary skills to interpret ECGs in exam scenarios and clinical practice.

Classical Approach to ECGs

RATE
- normal = 60-100 bpm (atrial rate: 150-250 bpm = paroxysmal tachycardia, 250-350 bpm = atrial flutter, >350 bpm = AFib)
- regular rhythm
  - to calculate the rate, divide 300 by number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 s)
or remember 300-150-100-75-60-50-43 (rate falls in this sequence with the number of large squares between 2 QRS complexes)

- irregular rhythm
  - rate = 6 x number of R-R intervals in 10 s (the “rhythm strips” are 10 s recordings)
  - types: wandering pacemaker, multifocal atrial tachycardia, AFib
  - atrial escape = 60-80 bpm; junctional escape = 40-60 bpm; ventricular escape = 20-40 bpm

**RHYTHM**

- regular: R-R interval is the same across the tracing
- irregular: R-R interval varies across the tracing
- regularly irregular: repeating pattern of varying R-R intervals
- irregularly irregular: R-R intervals vary erratically
- normal sinus rhythm (NSR)
  - P wave precedes each QRS; QRS follows each P wave
  - P wave axis is normal (positive in leads I, aVF)
  - rate between 60-100 bpm

**AXIS**

- mean axis indicates the direction of the mean vector
- can be determined for any waveform (P, QRS, T)
- the standard ECG reported QRS axis usually refers to the mean axis of the frontal plane – it indicates the mean direction of ventricular depolarization forces
- QRS axis in the frontal plane
  - normal axis: -30º to 90º (i.e. positive QRS in leads I and II)
  - left axis deviation (LAD): axis <-30º
  - right axis deviation (RAD): axis >90º
- QRS axis in the horizontal plane is not routinely calculated – it is directed posteriorly and to the left
  - transition from negative to positive is usually in lead V3

**Table 1. Conduction Abnormalities**

<table>
<thead>
<tr>
<th>Left Bundle Branch Block (LBBB)</th>
<th>Right Bundle Branch Block (RBBB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete LBBB</td>
<td>Complete RBBB</td>
</tr>
<tr>
<td>QRS duration &gt;120 msec</td>
<td>QRS duration &gt;120 msec</td>
</tr>
<tr>
<td>Broad notched or slurred R waves in leads I, aVL, and usually V5 and V6</td>
<td>Positive QRS in lead V1 (rSR' or occasionally broad R wave)</td>
</tr>
<tr>
<td>Deep broad S waves in leads V1-2</td>
<td>Broad S waves in leads I, V5-6 (&gt;40 msec)</td>
</tr>
<tr>
<td>Secondary ST/T changes (+ve in leads with broad R waves, +ve in V1-2)</td>
<td>Usually secondary T wave inversion in leads V1-2</td>
</tr>
<tr>
<td>LBBB can mask ECG signs of MI</td>
<td></td>
</tr>
</tbody>
</table>

**Left Anterior Fascicular Block (LAFB)**

<table>
<thead>
<tr>
<th>Left Anterior Hemiblock</th>
<th>Left Posterior Fascicular Block (LPFB)</th>
<th>Bifascicular Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Axis Deviation (-30º to -90º)</td>
<td>Right Axis Deviation (110º to 180º)</td>
<td>RBBB pattern</td>
</tr>
<tr>
<td>Small q and prominent R in leads I and aVl</td>
<td>Small r and prominent S in leads II, III, and aVl</td>
<td>Small q and prominent R</td>
</tr>
<tr>
<td>Small r and prominent S in leads II, III, and aVl</td>
<td>Small q and prominent R in leads II, III, and aVl</td>
<td>The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB</td>
</tr>
<tr>
<td>RBBB pattern refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Nonspecific Intraventricular Block**

- QRS duration >120 msec
- absence of criteria for LBBB or RBBB
Table 2. Hypertrophy/Chamber Enlargement

Left Ventricular Hypertrophy (LVH) | Right Ventricular Hypertrophy (RVH)
--- | ---
• S in V1 + R in V5 or V6 > 35 mm above age 40, (>40 mm for age 31-40, >45 mm for age 21-30)  
• R in aVL > 11 mm  
• R in I + S in III > 25 mm  
• Additional criteria:  
  ▪ LV strain pattern (ST depression and T wave inversion in leads I, aVL, V4-V6)  
  ▪ Left atrial enlargement  
• Right axis deviation  
• R/S ratio > 1 or qR in lead V1  
• RV strain pattern: ST segment depression and T wave inversion in leads V1-2

Left Atrial Enlargement (LAE) | Right Atrial Enlargement (RAE)
--- | ---
• Biphasic P wave with the negative terminal component of the P wave in lead V1 ≥ 1 mm wide and ≥ 1 mm deep  
• P wave > 120 msec, notched in lead II (“P mitrale”)  
• P wave > 2.5 mm in height in leads II, III, or aVF (“P pulmonale”)  
• Biphasic P wave with the negative terminal component of the P wave in lead V1 ≥ 1 mm wide and ≥ 1 mm deep  
• P wave > 120 msec, notched in lead II (“P mitrale”)  
• P wave > 2.5 mm in height in leads II, III, or aVF (“P pulmonale”)  
• Additional criteria:  
  ▪ Left atrial enlargement

ISCHEMIA/INFARCTION

• Look for the anatomic distribution of the following ECG abnormalities (see Table 3)
  
  ▪ Ischemia  
    ▪ ST segment depression  
    ▪ T wave inversion (most commonly in V1-V6)
  
  ▪ Injury  
    ▪ Transmural (involving the epicardium)  
      ▪ ST elevation in the leads facing the area injured/infarcted  
      ▪ Transient ST elevation may occur in patients with coronary artery spasm  
        (e.g. Prinzmetal angina) which can be slight or prominent (>10 mm)  
    ▪ Subendocardial  
      ▪ Marked ST depression in the leads facing the affected area  
      ▪ May be accompanied by enzyme changes and other signs of MI  
      ▪ May also occur with angina

Figure 10. Typical ECG changes with infarction

• Evolving infarction (ST elevation in contiguous leads = acute MI)
  
  ▪ “Typical” sequential changes of evolving MI  
    1. Hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
    2. ST elevation (injury pattern) in the leads facing the infarcted area  
      ▪ Usually in the first hours post infarct  
      ▪ In acute posterior infarction, there is depression in V1-V3 (reciprocal to ST elevation in the posterior leads, that are not recorded in the standard 12-lead ECG)  
    3. Significant Q waves: > 40 msec or > 1/3 of the total QRS (hours to days post-infarct)
    4. Inverted T waves (one day to weeks after infarction)  
      ▪ This classical sequence does not always occur  
      ▪ Q waves of infarction may appear in the very early stages, with or without ST changes  
      ▪ Non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction
  
  ▪ Completed infarction  
    ▪ Abnormal Q waves (wide Q waves may be found in III and aVL in normal individuals)  
      ▪ Duration > 40 msec (> 30 msec in aVF for inferior infarction)  
      ▪ Q/QRS voltage ratio is > 33%  
    ▪ Abnormal R waves (R/S ratio > 1, duration > 40 msec) in V1 and more frequently in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)
Table 3. Areas of Infarction (Q wave)/Ischemia (in right dominant anatomy)

<table>
<thead>
<tr>
<th>Vessel Usually Involved</th>
<th>Infarct Area (LAD and LC)</th>
<th>Leads (LAD and LC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending (LAD)</td>
<td>Anteroseptal</td>
<td>V1, V2</td>
</tr>
<tr>
<td></td>
<td>Anterior</td>
<td>V2, V4</td>
</tr>
<tr>
<td></td>
<td>Anterolateral</td>
<td>I, aVL, V3-6</td>
</tr>
<tr>
<td></td>
<td>Extensive anterior</td>
<td>I, aVL, V1-6</td>
</tr>
<tr>
<td>Right coronary artery (RCA)</td>
<td>Inferior</td>
<td>II, III, aVF</td>
</tr>
<tr>
<td></td>
<td>Right ventricle</td>
<td>V3R, V4R (right sided chest leads)</td>
</tr>
<tr>
<td></td>
<td>Posterior MI (assoc. with inf. MI)</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
<tr>
<td>Left circumflex (LCX)</td>
<td>Lateral</td>
<td>I, aVL, V5-6</td>
</tr>
<tr>
<td></td>
<td>Isolated posterior MI</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
</tbody>
</table>

MISCELLANEOUS ECG CHANGES

Electrolyte Disturbances
- hyperkalemia
  - mild to moderate (K⁺ 5-7 mmol/L): tall peaked T waves
  - severe (K⁺ >7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show bizarre patterns, axis shifts left or right, ST shift with tall T waves, eventually becomes a “sine wave” pattern
- hypokalemia
  - ST segment depression, prolonged QT interval, low T waves, prominent U waves (U>T)
  - enhances the toxic effects of digitalis
- hypercalcemia
  - shortened QT interval (more extracellular Ca²⁺ means shorter plateau in cardiac action potential)
- hypocalcemia
  - prolonged QT interval (less extracellular Ca²⁺ means longer plateau in cardiac action potential)

![Figure 11. Hyperkalemia](image1)

![Figure 12. Hypokalemia](image2)

Figure 11. Hyperkalemia

Figure 12. Hypokalemia

Hypothermia
- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- AFib with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves: “hump-like” waves at the junction of the J point and the ST segment

Pericarditis
- early: diffuse ST segment elevation ± PR segment depression, upright T waves
- later: isoelectric ST segment, flat or inverted T waves
- ± tachycardia

Drug Effects
- digitalis
  - therapeutic levels may be associated with “digitalis effect”:
    - ST downsloping or “scooping”
    - T wave depression or inversion
    - QT shortening ± U waves
    - slowing of ventricular rate in AFib
  - toxic levels associated with
    - arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradycardia in AFib, accelerated junctional rhythms, PVCs, ventricular tachycardia (see Arrhythmias, C15)
    - “regularization” of ventricular rate in AFib due to a junctional rhythm and AV dissociation
    - amiodarone, quinidine, phenothiazines, tricyclic antidepressants, antipsychotics, some antihistamines, some antibiotics: prolonged QT interval, U waves

Low Voltage
- Definition: total QRS height in precordial leads <10 mm and/or limb leads <5 mm
- Differential diagnosis
  - Myocardial disease
  - Ischemia
  - Cardiomyopathy (usually infiltrative type), myocarditis
  - Pericardial effusion
  - Thick chest wall/barrel chest: COPD, obesity
  - Generalized edema
  - Hypothyroidism/myxedema
  - Inappropriate voltage standardization

![Figure 13. Osborne J waves of a hypothermic patient](image3)

Digitalis Side Effects
- Palpitations, fatigue, visual changes (yellow vision), decreased appetite, hallucinations, confusion, and depression

Pacemakers
- Demand pacemaker has discharge (narrow vertical spike on ECG strip) prior to widened QRS
- Atrial pacemaker has discharge prior to P wave
- Triggered pacemaker has discharge following the P wave but prior to the widened QRS
- Atrial and ventricular pacing have discharge before the P wave and widened QRS wave
Figure 14. Atrial fibrillation, ST change due to digitalis ("digitalis effect")

Pulmonary Disorders
- cor pulmonale (often secondary to COPD)
  - low voltage, RAD, poor R wave progression
  - RAE and RVH with strain
  - multifocal atrial tachycardia (MAT)
- massive PE
  - sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  - RAD, RVH with strain – most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III)

Alternative PQRSTU Approach to ECGs

Note: The information seen in this alternative approach – the PQRSTU Approach – is the same as the information in the Classical Approach. It is just organized in a slightly different way based on the Anatomy of the ECG.

Figure 15. ECG correlations with heart activity

P WAVE
- the P wave provides a view into the atria of the heart and represents atrial contraction
- the best leads to view the P waves are II and V1
- assess the P waves for rate (based on the P-P interval relative to the R-R interval), rhythm (rounded, flutter/sawtooth, fibrillation) and axis
- lead II: the P wave should be rounded, <120 msec and <2.5 mm in height
- lead V1: the P wave is biphasic with a negative phase slightly greater than the positive phase
Common P Wave Pathology
- atrial flutter: sawtooth P wave (HINT: flip the ECG upside-down to see it better if unclear)
- atrial fibrillation: absent P wave, may have fibrillatory wave, irregular rhythm
- right atrial enlargement: tall P wave (>2.5 mm) in II or V1 (P pulmonale)
- left atrial enlargement: negative deflection >1 mm deep or >1 mm wide in V1, wide (>120 msec) notched P wave in II (P mitrale)

P-R INTERVAL
- the P-R interval shows the delay between atrial and ventricular contraction that is mediated by the AV node; the magnitude of the delay is referred to as “dromotropy”
- positive dromotropy increases conduction velocity (e.g. epinephrine stimulation), negative dromotropy decreases velocity (e.g. vagal stimulation)
- P-R interval should be 120-200 msec
- long P-R interval (>200 msec)
  - heart block: first degree (fixed, prolonged P-R interval), second degree Mobitz I/Wenckebach (steadily prolonging to eventual dropped beat)
  - heart block
    - first degree: fixed, prolonged P-R interval
    - second degree Mobitz I/Wenckebach: steadily prolonging P-R interval to eventual dropped beat
    - second degree Mobitz II/Hay: fixed P-R interval with ratio of beat to dropped beat (e.g. for every 3 beats, there is one dropped beat [3:1])
  - third degree/complete: variable P-R intervals, P-P and R-R intervals individually constant but not in sync
  - atrial flutter
  - sinus bradycardia (normal to have long P-R if heart rate slow)
  - hypokalemia
  - trifascicular block
- short P-R interval (<120 msec)
  - pre-excitation syndrome (delta wave: upswooping of the P-R segment into the QRS complex indicating pre-excitation)
  - accessory pathways
  - WPW

QRS COMPLEX
- the QRS is where ventricular contraction is visualized
- rate: check the R-R interval to see if it matches the PP interval
- amplitude: check for hypertrophy (see Table 2, C7)
- narrow width (<120 msec) QRS means that the His-Purkinje system is being used
- wide width (>120 msec) QRS means that the His-Purkinje system is being bypassed or is diseased
  - BBB, VT, ventricular hypertrophy, cardiomyopathy, WPW, ectopic ventricular beat, hyperkalemia, drugs (e.g. TCAs, antiarrhythmics)
  - Q wave: the first downward deflection of the QRS complex
    - significant Q wave: ≥ 40 msec or >33% of total QRS amplitude; indicate myocardial necrosis (new or historical)
  - R and S wave abnormalities typically show pathology in terms of BBB or intraventricular abnormalities

ST SEGMENT
- one of the more famous ECG personas mostly due to its role in detecting MI
- located between QRS complex and the T wave
- corresponds to the completion of ventricular depolarization
- normally at the same level as “baseline/TP segment”
- ST elevation: at least 1 mm in 2 adjacent limb leads or at least 1-2 mm in adjacent precordial leads in STEMI (signifies occlusion and transmural ischemic injury) vs. diffuse pattern in early periocarditis
- ST depression: ischemia
  - ischemia which causes ST depression can result in myocardial damage (NSTEMI)
  - lateral wall ST depression (leads I, aVL, V5, V6) may actually indicate a STEMI in the right heart

T WAVE
- this is the repolarization phase of the ventricles (repolarization of the atria are obscured by the QRS complex)
- typically positive (except in aVR and V1) on ECG but normal isolated negative T waves may be present
- pathology when T wave variation occur in consecutive leads
  - inversion: BBB, ischemia, hypertrophy, drugs (e.g. digitalis), pulmonary embolism (lead III as part of S1Q3T3 sign)
- elevation: infarction (STEMI, Prinzmetal, hyperacute), hyperkalemia (wider, peaked)
- flattened: hypokalemia, pericarditis, drugs (e.g. digitalis), pericardial effusion
- variations: T wave alters; beat-to-beat variations due to PVC overlap (R on T phenomenon which may precipitate VT or VFib)
- appropriate T wave discordance: in BBB, T wave deflection should be opposite to that of the normal QTc is 360-450 msec for males and 360-460 for females
- corrected QT (QTc) is often used instead in practice to correct for the repolarization duration; this represents the duration of ventricular depolarization and repolarization and is often difficult to interpret
- appropriate T wave discordance suggests ischemia or infarction

Q-T INTERVAL
- this represents the duration of ventricular depolarization and repolarization and is often difficult to interpret
- corrected QT (QTc) is often used instead in place to correct for the repolarization duration: 
  \[ QTc = \frac{QT}{\sqrt{RR}} \]
- normal QTc is 360-450 msec for males and 360-460 for females
- increased (>450 msec for males and >460 for females): risk of Torsades de Pointes (a lethal tachyarrhythmia)
  - genetic Long QT Syndrome (often a channelopathy)
  - drugs: antibiotics, SSRIs, antipsychotics, antiarrhythmics
  - electrolytes: low Ca²⁺, low Mg²⁺, low K⁺
  - others: hypothyroidism, hypothermia, cardiomyopathy
- decreased (<360 msec): risk of VFib
  - electrolytes: high Ca²⁺
  - drugs: digoxin
  - others: hyperthyroidism

U WAVE
- origin unclear but may be repolarization of Purkinje fibers or delayed/prolonged repolarization of the myocardium
- more visible at slower heart rates
- deflection follows T wave with <25% of the amplitude
- variations from norm could indicate pathologic conditions:
  - prominent (>25% of T wave): electrolyte (low K⁺), drugs (digoxin, antiarrhythmics)
  - inverted (from T wave): ischemia, volume overload

Cardiac Biomarkers
- provide diagnostic and prognostic information in acute coronary syndromes and in heart failure

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Peak</th>
<th>Duration Elevated</th>
<th>DDx of Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin T</td>
<td>1-2 d</td>
<td>Up to 2 wk</td>
<td>MI, CHF, AFib, acute PE, myocarditis, chronic renal insufficiency, sepsis, hypovolemia</td>
</tr>
<tr>
<td>CK-MB</td>
<td>1 d</td>
<td>3 d</td>
<td>MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, chronic renal insufficiency, etc.</td>
</tr>
</tbody>
</table>

Ambulatory ECG
- indications for outpatient testing: palpitations, syncope, antiarrhythmic drug monitoring, arrhythmia surveillance in patients with documented or potentially abnormal rhythms, and surveillance of non-sustained arrhythmias that can lead to prophylactic intervention
- available technologies
  - Holter monitor
    - battery operated, continually records up to 3 leads for 24-48 h
    - symptoms recorded by patient on Holter clock for correlation with ECG findings
    - continuous loop recorder (diagnostic yield 66-83%)
    - worn continuously and can record data before and after patient activation for symptomatic episodes (usually worn for 2 wk)

Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea

Population: 452 patients (mean age 71 yr, 58% male) with acute dyspnea; patients with severe renal disease or cardiogenic shock were excluded.

Intervention: Assessment including measurement of B-type natriuretic peptide or standard assessment.

Outcome: Time to discharge and total cost of treatment.

Results: Median time to discharge was significantly shorter in the intervention group when compared with the control group (6.0 vs. 11.0 d, p=0.001).

Conclusions: In patients with acute dyspnea, measurement of B-type natriuretic peptide significantly reduced the need for admission to hospital and intensive care. The 30-d mortality rates were similar (10% vs. 12%, p=0.45).
- external and implantable devices
  - external devices can be transtelephonically downloaded
  - implantable loop recorder (ILR): cannot be transtelephonically downloaded; left in place for 14 to 18 mo

**Echocardiography**

**Transthoracic Echocardiography**
- ultrasound beams are directed across the chest wall to obtain images of the heart
- indications: evaluation of LVEF, wall motion abnormalities, myocardial ischemia and complications of MI, chamber size, wall thickness, valve morphology, proximal great vessel morphology, pericardial effusion, unexplained hypotension, murmurs, syncope, congenital heart disease
- use with Doppler to quantify degree of valvular stenosis or regurgitation

**Transoesophageal Echocardiography**
- ultrasound probe inserted into the esophagus to allow for better resolution of the heart and structures
- better visualization of posterior structures, including left atrium, mitral and aortic valves, interatrial septum
- invasive procedure used to complement transthoracic echocardiography
- indications: intracardiac thrombi, tumors, valvular vegetations (infective endocarditis), aortic dissection, aortic atheromas, prosthetic valve function, shunt, technically inadequate transthoracic study
- use with Doppler to quantify degree of valvular stenosis or regurgitation

**Stress Echocardiography**
- echocardiography in combination with either physiologic (exercise treadmill or bike testing) or pharmacologic (dobutamine infusion) stress
- validated in demonstrating myocardial ischemia and assessing viability
- provides information on the global left ventricular response to exercise
- used for valvular heart disease evaluation

**Contrast Echocardiography**
- contrast agents injected into the bloodstream to improve imaging of the heart
- conventional agent: agitated saline (contains microbubbles of air)
- allows visualization of right heart and intracardiac shunts, most commonly patent foramen ovale (PFO) and sometimes intrapulmonary shunt
- newer contrast agents are capable of crossing the pulmonary bed and achieving left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders and enhance evaluation of LV ejection fraction, wall motion abnormalities, and intracardiac mass

**Stress Testing**

**EXERCISE TESTING**
- cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring
- guidelines for use
  - patients with intermediate (10-90%) pretest probability of CAD based on age, gender, and symptoms
  - ST depression <1 mm at rest, no left bundle branch block, no digoxin or estrogen use
  - exercise test results stratify patients into risk groups
  - low risk patients can be treated medically without invasive testing
  - intermediate risk patients may need additional testing in the form of exercise imaging studies or cardiac catheterization
  - high risk patients should be referred for cardiac catheterization

**Indications for Terminating Exercise Stress Test**
- drop in systolic blood pressure of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
- moderate to severe angina
- ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
- increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
- signs of poor perfusion (cyanosis or pallor)
- technical difficulties in monitoring ECG or systolic blood pressure
- patient's desire to stop
- sustained ventricular tachycardia

**Most Commonly Used Treadmill Stress Test Protocols**
- The Bruce Protocol: 7 stage test with each stage lasting 3 min. With each successive stage, the treadmill increases in both speed (2.7 km/h to 9.6 km/h) and grade (10% with a 2% increase per stage up to 22%)
- The Modified Bruce, Modified Naughton Protocol: for older individuals or those with limited exercise capacity

**Important Contraindications to Exercise Testing**
- Acute MI, aortic dissection, pericarditis, myocarditis, PE
- Severe AS, arterial HTN
- Inability to exercise adequately
Interpretation

- The most commonly used ECG criteria for a positive exercise test: ≥1 mm of horizontal or downsloping ST-segment depression or elevation (at least 60-80 msec after the end of the QRS complex).

Nuclear Cardiology

- Myocardial perfusion imaging (MPI) with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer.
- Evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously.
- Predicts the likelihood of further cardiac event rates independent of the patient’s history, examination, resting ECG, and stress ECG.
- Often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi).
- Stress with either treadmill or IV vasodilator stress (dipyridamole [Persantine®], adenosine).
- Images of the heart obtained during stress and at rest 3-4 h later.
- Fixed defect: impaired perfusion at rest and during stress (infarcted/hibernating).
- Reversible defect: impaired perfusion only during stress (ischemic).
- Tracers:
  - Thallium-201 (201Tl, a K⁺ analogue).
  - Technetium-99 (⁹⁹Tc)-labelled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®).

Stress Echocardiography

- See Stress Echocardiography, C12.

Indications for Stress Testing

- Exercise ECG:
  - Initial evaluation in patients who are able to exercise.
  - Exercise stress echo when ECG is uninterpretable.
  - Intermediate pre-test probability with normal/equivocal exercise ECG.
  - Post-ACS when used to decide on potential efficacy of revascularization.
  - To evaluate the clinical significance of valvular heart disease.

- Dobutamine stress echo (DSE):
  - Pharmacologic stress for patients who are physically unable to exercise; same indications as exercise stress echo.
  - Low dose DSE can be used to assess myocardial viability and for assessing aortic stenosis with LV systolic dysfunction.

- Exercise MPI:
  - When ECG is uninterpretable.
  - Intermediate pre-test probability with normal/equivocal exercise ECG.
  - In patients with previous imaging whose symptoms have changed.
  - To diagnose ischemia.

- Dipyridamole/Adenosine MPI:
  - To diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarkers.
  - When ECG is uninterpretable due to LBBB or V-paced rhythm.
  - Among patients unable to exercise, with the same indications as exercise MPI.

Cardiac Catheterization and Angiography

- Risks of procedure related complications: vascular injury (including dissection), renal failure, stroke, MI.
- Mortality rate 0.1-0.2%.
- Invasive: catheters are introduced percutaneously into arterial and venous circulation under conscious sedation and contrast is injected.
- Arterial access most commonly through the femoral artery; radial approach gaining favor especially for obese patients and outpatients dependent on driving and ambulation.
- Venous access through the femoral vein or internal jugular vein (for patients also undergoing right heart catheterization)
- Same day procedure as outpatient.
- Indications for prehospitalization: anticoagulation, renal failure, diabetes, contrast allergy.
- Catheterization permits direct measurement of intracardiac pressures, transvalvular and mean peak pressure gradients, valve areas, cardiac output, shunt data, oxygen saturations, and visualization of coronary arteries, cardiac chambers, and great vessels.
- Angiography may provide valuable information regarding lesion severity, complexity, location, and prognosis.

Important Prognostic Factor

Duke Treadmill Score (DTS)

Weighted Index Score:

- Treadmill exercise time using standard Bruce protocol.
- Maximum net ST segment deviation (depression or elevation).
- Exercise-induced angina is diagnostic and prognostic information (such as 1 yr mortality).

\[
DTS = \text{exercise time} - (5 \times \text{MaxST}) - (4 \times \text{angina index})
\]

Angina index: 0 (no angina), 1 (angina but not exercise-limiting), 2 (exercise-limiting angina).

- DTS ≥5: 0.25% 1 yr mortality.
- DTS 4 to -10: 1.25% 1 yr mortality.
- DTS ≤-11: 5.25% 1 yr mortality.


Patients with normal imaging (nuclear perfusion or stress echo) studies at peak stress have a <1%/yr incidence of death or nonfatal MI and are thus often spared further invasive evaluation.
Right Heart Catheterization (Swan-Ganz Catheter)
- right atrial, right ventricular, and pulmonary artery pressures are recorded
- can also be used to measure the Cardiac Index (CI)
  - CI = CO/Body Surface Area
  - cardiac index is a measure of cardiac function
    - <1.8 L/min/m² usually means cardiogenic shock
    - 2.6-4.2 L/min/m² is considered normal
- pulmonary capillary wedge pressure (PCWP)
  - obtained by advancing the catheter to wedge in the distal pulmonary artery
  - records pressure measured from the pulmonary venous system
  - in the absence of pulmonary venous disease reflects left atrial pressure

Figure 17. Swan-Ganz catheter placement

Left Heart Catheterization
- systolic and end-diastolic pressure tracings recorded
- LV size, wall motion and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
- cardiac output (measured by the Fick oxygen method or the indicator dilution method)

Coronary Angiography
- coronary vasculature accessed via the coronary ostia
- contraindicated in severe renal failure (due to contrast agent toxicity) – must check renal status

Figure 18. Coronary angiogram schematic
AM = acute marginal; LAD = left anterior descending; OM = obtuse marginal; RCA = right coronary artery

ACC/AHA 2011 Recommended Indications for Coronary Angiography
- Disabling (CCS classes III and IV) chronic stable angina despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Serious ventricular arrhythmia or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing

Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter
Diagnostic Catheterization

- complications for diagnostic catheterization <1%
- inadequate diagnostic procedures occur in fewer than 1% of cases
- provocative pharmacological agents can be used to unmask pathology
  - fluid loading may unmask latent pericardial constriction
  - afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient
  - coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  - a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, calcium channel blockers, adenosine, nitric oxide, or prostacyclin)

Contrast-Enhanced CT Coronary Angiography

- fast ECG-synchronized multi-slice CT image acquisition in the heart has enabled non-invasive imaging of the coronary arterial tree
- often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
- sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis

Magnetic Resonance Imaging

- offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
- valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, and assessment of viable myocardium

CARDIAC DISEASE

Arrhythmias

Mechanisms of Arrhythmias

(I) Alterations in Impulse Formation

A. Abnormal Automaticity

- automaticity is a property of certain cardiomyocytes to spontaneously depolarize to their threshold voltage to generate action potentials in a rhythmic fashion
- under normal circumstances only cells in the specialized conduction system (SA node, AV node, and ventricular conduction system) exhibit natural automaticity. These cells are pacemaking cells. The automaticity of these cells can become abnormally increased or decreased
- in disease (e.g. post-MI ventricular ischemia) cells in the myocardium outside the conduction system may inappropriately acquire the property of automaticity and contribute to abnormal depolarization. If these ectopic generators depolarize at a rate that is greater than the SA node, they assume pacemaking control and become the source of abnormal rhythm
- automaticity can be influenced by:
  - neurohormonal tone (sympathetic and parasympathetic stimulation)
  - abnormal metabolic conditions (hypoxia, acidosis, hypothermia)
  - electrolyte abnormalities
  - drugs (e.g. digitalis)
  - local ischemia/infarction
  - other cardiac pathology
- this mechanism is responsible for the accelerated idioventricular rhythm and ventricular tachycardia that often occurs 24-72 h post MI

B. Triggered Activity due to Afterdepolarizations

1. Early Afterdepolarizations

- occur in the context of action potential prolongation
- consequence of the membrane potential becoming more positive during repolarization (e.g. not returning to baseline)
- result in self-maintaining depolarizing oscillations of action potential, generating a tachyarrhythmia (e.g. new baseline voltage is greater than threshold, which automatically triggers a new action potential after the refractory period ends)
- basis for the degeneration of QT prolongation, either congenital or acquired, into Torsades de Pointes
2. Delayed Afterdepolarizations
   - occur after the action potential has fully repolarized, but before the next usual action potential, thus called a delayed afterdepolarization
   - commonly occurs in situations of high intracellular calcium (digitalis intoxication, ischemia) or during enhanced catecholamine stimulation (e.g. “twitchy” pacemaker cells)

(II) Alterations in Impulse Conduction
A. Re-Entry Circuits
   - the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium (see Figure 26, C21, for an example in the context of AV nodal re-entrant tachycardia)
     - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits

B. Conduction Block
   - ischemia, fibrosis, trauma, and drugs can cause transient, permanent, unidirectional or bidirectional block
   - most common cause of block is due to refractory myocardium (cardiomyocytes are in refractory period or zone of myocardium unexcitable due to fibrosis)
   - if block occurs along the specialized conduction system distal zones of the conduction system can assume pacemaking control
   - conduction block can lead to bradycardia or tachycardia when impaired conduction leads to re-entry phenomenon

C. Bypass Tracts
   - normally the only conducting tract from the atria to the ventricles is the AV node into the His-Purkinje system
   - congenital/acquired accessory conducting tracts bypass the AV node and facilitate premature ventricular activation before normal AV node conduction
   - see Pre-Excitation Syndromes, C21

---

**Arrhythmias**

**Bradyarrhythmias (<60 bpm)**
- Sinus bradycardia
- Sinoatrial block
- AV block (2nd and 3rd degree)
- Junctional rhythm
- Idioventricular rhythm

**Tachyarrhythmias (>100 bpm)**
- Regular
  - Narrow QRS (SVTs)
    - Sinus tachycardia
    - Atrial tachycardia
    - Junctional tachycardia
    - AVNRT
    - AVRT (orthodromic)
    - Atrial flutter
  - Wide QRS
    - SVT with aberrancy/BBB
    - Ventricular tachycardia
    - AVRT (antichronic)
- Irregular
  - Narrow QRS (SVTs)
    - Atrial fibrillation
    - A. flutter with variable block
    - Multifocal atrial tachycardia
    - Premature atrial contraction
  - Wide QRS
    - Atrial fibrillation with BBB
    - A. flutter with BBB and variable block
    - Polymorphic VT (torsades)
    - Premature ventricular contraction

**SA NODAL DYSFUNCTION**

**Sinus Bradycardia**
- P axis normal (P waves positive in I and aVF)
- rate <60 bpm
- marked sinus bradycardia (<50 bpm) may be seen in normal adults, particularly athletes, and in elderly individuals
- caused by
  - increased vagal tone or vagal stimulation
  - vomiting
  - episodes of myocardial ischemia or infarction (inferior MI)
  - sick sinus syndrome
  - increased intracranial pressure
  - hypothyroidism
  - hypothermia
  - drugs (β-blockers, calcium channel blockers, etc.)
• treatment: if symptomatic, atropine during acute episodes; pacing for sick sinus syndrome; if drug-induced, reduction or withdrawal of drugs

Sinus Block, Pause, and Arrest
• three disorders involving the SA node in which the sinus pacemaker fires but the impulse fails to depolarize the atrial myocardium resulting in no initial P wave (and consequently no QRS complex, ST segment, or T wave)
• sinus block (SA block): a complete block or failure of the sinus node to depolarize the atria; the block can last one or more cardiac cycles and is a multiple of the normal P-P interval
• sinus pause: a delay in the formation of a sinus impulse in the SA node resulting in a temporary pause (usually >3 s)
• sinus arrest: a longer delay in the formation of a sinus impulse in the SA node
  ▪ there is no clear-cut off between sinus pause vs. arrest – if the pause lasts greater than 3x the normal P-P interval it may be called an arrest
  ▪ the P-P prolongation is not phasic or gradual (unlike sinus arrhythmia) and is not a multiple of the normal P-P interval (unlike sino-atrial block)
• escape beats or rhythm may occur:
  ▪ atrial escape: P waves with abnormal morphology
  ▪ junctional escape: P waves not seen, or follow the QRS (retrograde P), rate 40-60 bpm
  ▪ ventricular escape: no P wave; wide, abnormal QRS; slow rate 20-40 bpm

Sick Sinus Syndrome
• characterized by sinus node dysfunction (marked bradycardia, sinus pause/arrest, sinoatrial block), mainly in the elderly
  ▪ when symptomatic, electronic pacemaker is indicated
• frequently associated with episodes of atrial tachyarrhythmias ("tachy-brady syndrome")
• usually require a combination of a pacemaker for bradycardia and medications (β-blocker, calcium channel blocker, and/or digoxin, initiated after pacemaker insertion) for tachycardia

AV Conduction Blocks

First Degree AV Block
• prolonged PR interval (>200 msec)
• frequently found among otherwise healthy adults
• no treatment required

Second Degree AV Block
• some of the atrial impulses are not conducted to the ventricles
• can describe block by ratio of number of P waves to number of QRS (e.g. 2:1, 3:1, 4:1 increases in severity)
• second degree AV block is further subdivided into Type I and Type II block:
  ▪ Type I (Mobitz I) second degree AV block
    • a gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
    • AV block is usually in AV node (proximal)
      – triggers (usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia
      – not an indication for temporary or permanent pacing
  ▪ Type II (Mobitz II) second degree AV block
    • the PR interval is constant; there is an abrupt failure of conduction of a P wave
    • AV block is usually distal to the AV node (i.e. bundle of His)
    • increased risk of high grade or 3rd degree AV block

Figure 20. Second degree AV block with Wenckebach phenomenon (Mobitz I) (4:3 conduction) (lead V1)

Figure 21. Second degree AV block (Mobitz II) (3:2 conduction) (lead V1)
2:1 AV Block
• often not possible to determine whether the block is type I or type II
• prolonged or repeated recordings may clarify the diagnosis

Figure 22. 2:1 AV block (lead II)

Third Degree AV Block
• complete failure of conduction of the supraventricular impulses to the ventricles
• ventricular depolarization initiated by an escape pacemaker distal to the block
• QRS can be narrow or wide (junctional vs. ventricular escape rhythm)
• P-P and R-R intervals are constant, variable PR intervals
• no relationship between P waves and QRS complexes (P waves "marching through")
• management (see Electrical Pacing, C24)

Figure 23. Third degree AV block (complete heart block) (lead II)

Supraventricular Tachyarrhythmias
Presentation for SVT (and pre-excitation syndromes)
• presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
• may precipitate CHF, hypotension, or ischemia in patients with underlying disease
• untreated tachycardias can cause cardiomyopathy (rare, potentially reversible with treatment of SVTs)
• includes supraventricular and ventricular rhythms

Supraventricular Tachyarrhythmias
• tachyarrhythmias that originate in the atria or AV junction
• this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
• characterized by narrow QRS, unless there is pre-existing bundle branch block or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

Sinus Tachycardia
• sinus rhythm with rate >100 bpm
• occurs in normal subjects with increased sympathetic tone (exercise, emotions, pain), alcohol use, caffeinated beverages, drugs (e.g. β-adrenergic agonists, anticholinergic drugs, etc.)
• etiology: fever, hypotension, hypovolemia, anemia, thyrotoxicosis, CHF, MI, shock, PE, etc.
• treatment: treat underlying disease; consider β-blocker if symptomatic, calcium channel blocker if β-blockers contraindicated

Premature Beats
• premature atrial contraction
  ▪ ectopic supraventricular beat originating in the atria
  ▪ P wave morphology of the PAC usually differs from that of a normal sinus beat
• junctional premature beat
  ▪ ectopic supraventricular beat that originates in the vicinity of the AV node
  ▪ P wave is usually not seen or an inverted P wave is seen and may be before or closely follow the QRS complex (referred to as a retrograde, or "traveling backward" P wave)
• treatment usually not required

Atrial Flutter
• rapid, regular atrial depolarization from a macro re-entry circuit within the atrium (most commonly the right atrium)
• atrial rate 250-350 bpm, usually 300 bpm
• AV block usually occurs; it may be fixed (2:1, 3:1, 4:1, etc.) or variable
• etiology: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis
• ECG: sawtooth flutter waves (most common type of flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy); commonly see HR of 150

Figure 24. Atrial flutter with variable block
• in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and bring out flutter waves
• treatment of acute atrial flutter
  • acute and if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  • if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  • if stable
    (1) rate control: β-blocker, diltiazem, verapamil, or digoxin
    (2) chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
  • anticoagulation guidelines same as for patients with AFib
• treatment of long-term atrial flutter: antiarrhythmics, catheter radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter – i.e. whether right-sided isthmus-dependent or left-sided origin)

Multifocal Atrial Tachycardia
• irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
• atrial rate 100-200 bpm – at least 3 distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
• occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline, or digitalis toxicity
• treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
• no role for electrical cardioversion, antiarrhythmics, or ablation

Atrial Fibrillation
• see 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation for details
• most common sustained arrhythmia
• incidence increases with age (10% of population >80 yr old)
• see 2014 AHA/ACC/HRS guideline for the management and care of patients with atrial fibrillation

Multifocal Atrial Tachycardia
• irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
• atrial rate 100-200 bpm – at least 3 distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
• occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline, or digitalis toxicity
• treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
• no role for electrical cardioversion, antiarrhythmics, or ablation

Table 5. CHADS2 Risk Prediction for Non-Valvular AFib and Refer to AHA/ACC/HRS AFib Guidelines 2014 for more details

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS2 Score</th>
<th>Stroke Risk (%/Yr)</th>
<th>Anticoagulation Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
<td>0</td>
<td>1.9 (low)</td>
<td>ASA 81-325 mg OD</td>
</tr>
<tr>
<td>HTN</td>
<td>1</td>
<td>1</td>
<td>2.8 (low-mod)</td>
<td>oral anticoagulants*</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>1</td>
<td>2-3</td>
<td>4.0-5.9 (mod)</td>
<td>oral anticoagulants*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>4-6</td>
<td>8.5-18.2 (high)</td>
<td>oral anticoagulants*</td>
</tr>
<tr>
<td>Stroke/TIA (prior)</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Oral anticoagulants: “currently includes warfarin (INR 2-3) and direct oral anticoagulants (DOACs) e.g. apixaban, dabigatran, rivaroxaban

CHADS2 = 1.5; Patients either had previous thromboembolism or ≥3 risk factors.

ROCKET-AF Trial
NEJM 2011;365:883-891

Study: Prospective, non-inferiority, double blind, RCT, median follow-up of 1.9 yr.

Population: 14,264 patients with AFib (mean CHADS2 = 1.5). Patients either had previous thromboembolism or ≥3 risk factors.

Intervention: Patients were randomized to receiving rivaroxaban or warfarin.

Outcome: Composite of strokes and systemic thromboembolic event (STE).

Results: The hazard ratio of the primary outcome for rivaroxaban compared to warfarin was 0.89; 95% CI 0.74-1.03; p=0.001 for noninferiority; p=0.12 for superiority. Furthermore, the hazard ratio for major and non-major, but clinically relevant, bleeding was 1.03; 95% CI 0.96-1.11; p=0.44. There were also significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, p=0.02) and fatal bleeding (0.2% vs. 0.5%, p=0.003) for rivaroxaban.

Conclusions: In patients with AFib, rivaroxaban is non-inferior to warfarin for stroke prevention and major and non-major bleeding.
A Fib on ECG
- no organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline
- irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
- wide QRS complexes due to aberrancy may occur following a long-short cycle sequence ("Ashman phenomenon")
- loss of atrial contraction, thus no “a” wave seen in JVP; no S4 on auscultation

Figure 25. Atrial fibrillation (lead II)

Management

Major objectives (RACE): all patients with AF (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk and for the risk of bleeding, and most patients should receive either an oral antiocoagulant or ASA (see Table 5)
1. Rate control: β-blockers, diltiazem, verapamil (in patients with heart failure: digoxin, amiodarone)
2. Anticoagulation: use either warfarin or direct oral anticoagulant (DOACs) e.g. apixaban, dabigatran, rivaroxaban, to prevent thromboembolism
3. Cardioversion (electrical)
   - if A Fib <24-48 h, can usually cardiovert without anticoagulation if at low thromboembolic risk
   - if A Fib >24-48 h, anticoagulate for 3 wk prior and 4 wk after cardioversion due to risk of unstable intra-atrial thrombus
   - if patient unstable (hypotensive, active angina due to tachycardia, uncontrolled heart failure) should cardiovert immediately
4. Etiology
   - HTN, CAD, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, postoperative, PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol ("holiday heart")
   - may present in young patients without demonstrable disease ("Lone A Fib") and in the elderly without underlying heart disease

Additional Management Points Regarding A Fib
- studies of patients with A Fib suggest that there is no difference in long-term survival when treating patients with a rhythm-control vs. rate-control strategy
- however, many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate A Fib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible

Newly Discovered A Fib
- anticoagulants may be beneficial if high risk for stroke
- if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
- if A Fib persists, 2 options
  1. rate control and anticoagulation (as indicated above)
  2. cardioversion (as above)

Recurrent A Fib/Permanent A Fib
- if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
- patients who have undergone at least one attempt to restore sinr rhythm may remain in AFib after recurrence; permanent A Fib may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations
- if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
  - no or minimal heart disease: flecainide, propafenone, or sotalol
  - LV dysfunction: amiodarone
  - CAD: β-blockers, amiodarone

AV Nodal Re-Entrant Tachycardia
- re-entrant circuit using dual pathways (fast conducting β-fibers and slow conducting α-fibers) within or near the AV node; often found in the absence of structural heart disease – cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset
- fast regular rhythm: rate 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
• AVNRT accounts for 60-70% of all paroxysmal SVTs
• retrograde P waves may be seen but are usually lost in the QRS complex
• treatment
  ▪ acute: Valsalva or carotid massage, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina, or CHF)
  ▪ long-term: 1st line – β-blocker, diltiazem, digoxin; 2nd line – flecainide, propafenone; 3rd line – catheter ablation

Wolff-Parkinson-White Syndrome
• congenital defect present in 1.5-2/1,000 of the general population
• an accessory conduction tract (Bundle of Kent; can be in right or left atrium) abnormally allows early electrical activation of part of one ventricle
• impulses travel at a greater conduction velocity across the Bundle of Kent thereby effectively ‘bypassing’ AV node
• since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex – the so-called “delta wave”
• atrial impulses that conduct to the ventricles through both the Bundle of Kent and the normal AV node/His-Purkinje system generate a broad “fusion complex”
• ECG features of WPW
  ▪ PR interval <120 msec
  ▪ delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  ▪ widening of the QRS complex due to premature activation
  ▪ secondary ST segment and T wave changes
  ▪ tachyarrhythmias may occur – most often AVRT and AFib

AFib in WPW Patients
• AFib is the index arrhythmia in up to 20% of patients with WPW syndrome
  ▪ it is usually intermittent rather than persistent or permanent
• rapid atrial depolarizations in AFib are conducted through the bypass tract which is not able to filter impulses like the AV node can
• consequently the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens
• treatment: electrical cardioversion, IV procainamide, or IV amiodarone
  ▪ do not use drugs that slow AV node conduction (digoxin, β-blockers) as this may cause preferential conduction through the bypass tract and precipitate VF
• long-term: ablation of bypass tract if possible
AV Re-Entrant Tachycardia
- re-entrant loop via accessory pathway and normal conduction system
- initiated by a premature atrial or ventricular complex
- **orthodromic AVRT:** stimulus from a premature complex travels up the bypass tract (V to A) and down the AV node (A to V) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system)
  - comprises 95% of the reentrant tachycardias associated with WPW syndrome
- **antidromic AVRT:** more rarely the stimulus goes up the AV node (V to A) and down the bypass tract (A to V); wide and abnormal QRS as ventricular activation is only via the bypass tract
- **treatment**
  - acute: similar to AVNRT except avoid long-acting AV nodal blockers, e.g. digoxin and verapamil
  - long-term: for recurrent arrhythmias ablation of the bypass tract is recommended
    * drugs such as flecaïnide and procainamide can be used

Ventricular Tachyarrhythmias

Premature Ventricular Contraction (PVC) or Ventricular Premature Beat (VPB)
- QRS width >120 msec, no preceding P wave, bizarre QRS morphology
- origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
- PVCs may be benign but are usually significant in the following situations:
  - consecutive (≥3 = VT) or multiform (varied origin)
  - PVC falling on the T wave of the previous beat (“R on T phenomenon”): may precipitate ventricular tachycardia or VF

Accelerated Idioventricular Rhythm
- ectopic ventricular rhythm with rate 50-100 bpm
- more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
- frequently occurs in patients with acute MI or other types of heart disease (cardiomyopathy, hypertensive, valvular) but it does not affect prognosis and does not usually require treatment

Ventricular Tachycardia
- 3 or more consecutive ectopic ventricular complexes
  - rate >100 bpm (usually 140-200)
  - ventricular flutter: if rate >200 bpm and complexes resemble a sinusoidal pattern
  - "sustained VT" if it lasts longer than 30 s
  - ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec)
  - AV dissociation; bizarre QRS pattern
  - also favor Dx of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
  - occasionally during VT supraventricular impulses may be conducted to the ventricles generating QRS complexes with normal or aberrant supraventricular morphology (“ventricular capture”) or summation pattern (“fusion complexes”)
- **monomorphic VT**
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - typically result from intraventricular re-entry circuit
  - potential causes: chronic infarct scarring, acute MI/ischemia, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances
- **polymorphic VT**
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm) vs. monomorphic VT
  - potential causes: acute MI, severe or silent ischemia, and predisposing factors for QT prolongation (see *Torsades de Pointes, C23*)
- **treatment**
  - sustained VT (>30 s) is an emergency, requiring immediate treatment
  - hemodynamic compromise: electrical cardioversion
  - no hemodynamic compromise: electrical cardioversion, lidocaine, amiodarone, type Ib agents (procainamide, quinidine)
Table 6. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy*

<table>
<thead>
<tr>
<th>Clinical Clues</th>
<th>ECG Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms</td>
<td>AV dissociation</td>
</tr>
<tr>
<td>History of CAD and previous MI</td>
<td>Capture or fusion beats</td>
</tr>
<tr>
<td>Physical exam</td>
<td>QRS width &gt;140 msec</td>
</tr>
<tr>
<td>Cannon “a” waves</td>
<td>Extreme axis deviation</td>
</tr>
<tr>
<td>Carotid sinus massage/adenosine terminates arrhythmia</td>
<td>Positive QRS concordance (R wave across chest leads)</td>
</tr>
<tr>
<td></td>
<td>Negative QRS concordance ($S$ wave across chest leads) May suggest VT</td>
</tr>
</tbody>
</table>

*If patient >65 yr and previous MI or structural heart disease, then chance of VT >95%

**May terminate VT in some patients with no structural heart disease

Torsades de Pointes
- a variant of polymorphic VT that occurs in patients with baseline QT prolongation – “twisting of the points”
- looks like usual VT except that QRS complexes “rotate around the baseline” changing their axis and amplitude
- ventricular rate >100 bpm, usually 150-300 bpm
- etiology: predisposition in patients with prolonged QT intervals
  - congenital long QT syndromes
  - drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  - electrolyte disturbances: hypokalemia, hypomagnesemia
  - nutritional deficiencies causing above electrolyte abnormalities
- treatment: IV magnesium, temporary pacing, isoproterenol and correct underlying cause of prolonged QT, electrical cardioversion if hemodynamic compromise

Ventricular Fibrillation (VFib)
- chaotic ventricular arrhythmia, with very rapid irregular ventricular fibrillatory waves of varying morphology
- terminal event, unless advanced cardiac life-support (ACLS) procedures are promptly initiated to maintain ventilation and cardiac output, and electrical defibrillation is carried out
- most frequent cause of sudden death
- refer to ACLS algorithm for complete therapeutic guidelines

Electrophysiology Studies
- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradyarrhythmias: define the mechanisms of SA node dysfunction and localize site of AV conduction block
- tachyarrhythmias: map for possible ablation or to assess inducibility of VT
Electrical Pacing

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia in the setting of heart disease

Pacemaker Indications
- SA node dysfunction (most common): symptomatic bradycardia ± hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA node dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

Pacemaker Complications
- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism), pacemaker leads (perforation, malposition), pocket hematomas and infection
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure, pacemaker syndrome and pacemaker mediated tachycardia

Pacing Techniques
- temporary: transvenous (jugular, subclavian, femoral) or external (transcutaneous) pacing
- permanent: transvenous into RA, apex of RV, or both
- can sense and pace atrium, ventricle, or both
- new generation: rate responsive, able to respond to physiologic demand
- biventricular

Implantable Cardioverter Defibrillators

- sudden cardiac death (SCD) usually results from ventricular fibrillation (VFib), sometimes preceded by monomorphic or polymorphic ventricular tachycardia (VT)
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention
- benefit seen in patients with ischemic and non-ischemic cardiomyopathy, depressed left ventricular ejection fraction (LVEF), prolonged QRS
- see Heart Failure, C33 for current treatment recommendations

Catheter Ablation

Techniques
- radiofrequency (RF) energy: a low-voltage high-frequency form of electrical energy (similar to cautery); RF energy produces small, homogeneous, necrotic lesions approximately 3-7 mm in diameter and 3-5 mm in depth
- cryoablation: new technology which uses a probe with a tip that can decrease in temperature to -20°C and -70°C. Produces small, necrotic lesions similar to RF ablation. When brought to -20°C, the catheter tip reversely freezes the area. Bringing the tip down to -70°C for 5 min permanently scars the tissue
  - advantage: can “test” areas before committing to an ablation
  - disadvantage: takes much longer than RF (5 min per cryoablation vs. 1 min per RF ablation)

Indications
- paroxysmal SVT
  - AVNRT: accounts for more than half of all cases
- accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT
  - re-entrant rhythm, with an accessory AV connection as the retrograde limb
- corrected by targeting the accessory pathway
- atrial flutter: flutter focus in RA
- AFib: potential role for pulmonary vein ablation
- ventricular tachycardia: focus arises from the right ventricular outflow tract and less commonly originates in the inferoseptal left ventricle near the apex (note: majority of cases of VT are due to scarring from previous MI and cannot be ablated)

Major Complications
- 1% of patients
- death: 0.1-0.2%

Results:

ICDs reduced all-cause mortality by 54% (CI 37%-62%; P<0.01). The rate of ICD shocks was 5.3% (CI 4.1%-6.6%) in patients randomized to ICDs and 10.6% (CI 7.8%-13.4%) in the control group. Post-implantation complications included lead problems (1.5% CI 1.3%-1.8%); generator failure, pacemaker syndrome and pacemaker mediated tachycardia (0.3% CI 0.2%-0.4%). Rates of success of ICD implantation were 99% (CI 98.5%-99.3%) with a 16.5% (CI 15.2%-17.7%) rate of inappropriate shocks in ICD patients. Inappropriate shocks were documented in 0.3% (CI 0.2%-0.5%) of RCTs vs. 5% (CI 3.7%-7.2%) of observational studies. Rates of success of ICD implantation were 99% (CI 98.5%-99.3%) with a 16.5% (CI 15.2%-17.7%) rate of inappropriate shocks in ICD patients. Inappropriate shocks were documented in 0.3% (CI 0.2%-0.5%) of RCTs vs. 5% (CI 3.7%-7.2%) of observational studies. Rates of success of ICD implantation were 99% (CI 98.5%-99.3%) with a 16.5% (CI 15.2%-17.7%) rate of inappropriate shocks in ICD patients.
Ischemic Heart Disease

Epidemiology
- most common cause of cardiovascular morbidity and mortality
- atherosclerosis and thrombosis are the most important pathogenetic mechanisms
- M:F = 2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70
- according to the Framingham Heart Study, men develop coronary heart disease at a rate double that of women for age <60; incidence in women triples shortly after menopause
- peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women)
- for primary prevention of ischemic heart disease please see Family Medicine, FM7

Table 7. Risk Factors and Markers for Atherosclerotic Heart Disease

<table>
<thead>
<tr>
<th>Non-Modifiable Risk Factors</th>
<th>Modifiable Risk Factors</th>
<th>Markers of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Hyperlipidemia*</td>
<td>Elevated lipoprotein(a)</td>
</tr>
<tr>
<td>Male, postmenopausal female</td>
<td>Hypertension*</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Family history (FHx) of MI*</td>
<td>DM*</td>
<td>Elevated high-sensitivity C-reactive protein (hsCRP)</td>
</tr>
<tr>
<td>First degree male relative &lt;55</td>
<td>Cigarette smoking*</td>
<td>Coronary artery calcification</td>
</tr>
<tr>
<td>First degree female relative &lt;65</td>
<td>Metabolic syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sedentary lifestyle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heavy alcohol intake</td>
<td></td>
</tr>
</tbody>
</table>

* Major risk factor

Figure 34. Pathophysiology of atherosclerosis

Chronic Stable Angina

Definition
- symptom complex resulting from an imbalance between oxygen supply and demand in the myocardium

Etiology and Pathophysiology
- factors that decrease myocardial oxygen supply
  - decreased luminal diameter: atherosclerosis, vasospasm
  - decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - decreased hemoglobin: anemia
  - decreased SaO2: hypoxemia
  - congenital anomalies
• factors that increase myocardial oxygen demand  
  ▪ increased heart rate: hyperthyroidism  
  ▪ increased contractility: hyperthyroidism  
  ▪ increased wall stress: myocardial hypertrophy, aortic stenosis

Signs and Symptoms  
• typical: (1) retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/ arm/neck/jaw, associated with diaphoresis, nausea, anxiety; (2) predictably precipitated by the "3 Es": exertion, emotion, eating; (3) brief duration, lasting <10-15 min and typically relieved by rest and nitrates  
• atypical/probable angina (meets 2 of the above); non-cardiac chest pain (meets <1 of the above)  
• Levine’s sign: clenching fist over sternum when describing chest pain  
• anginal equivalents: dysnea, acute LV failure, flash pulmonary edema

Clinical Assessment  
• history including directed risk factor assessment and physical exam  
• labs: Hb, fasting glucose, fasting lipid profile  
• ECG (at rest and during episode of chest pain if possible)  
• CXR (suspected heart failure, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs or symptoms of pulmonary disease)  
• stress testing (see Cardiac Diagnostic Tests, C5) or angiography  
  ▪ echo  
  ▪ to assess systolic murmur suggestive of aortic stenosis, mitral regurgitation, and/or HCM  
  ▪ to assess LV function in patients with Hx of prior MI, pathological Q waves, signs or symptoms of CHF

Differential Diagnosis  
• see Differential Diagnoses of Common Presentations, CA

Treatment of Chronic Stable Angina

1. General measures  
  ▪ goals: to reduce myocardial oxygen demand and/or increase oxygen supply  
  ▪ lifestyle modification (diet, exercise)  
  ▪ treatment of risk factors: statins (see Endocrinology, E5, Family Medicine, FM9 for target lipid guidelines), antihypertensives, etc.  
  ▪ pharmacological therapy to stabilize the coronary plaque to prevent rupture and thrombosis

2. Antiplatelet therapy (first-line therapy)  
  ▪ ASA  
  ▪ clopidogrel when ASA absolutely contraindicated

3. β-blockers (first-line therapy – improve survival in patients with HTN)  
  ▪ increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)  
  ▪ cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β2 receptors)  
  ▪ avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand

4. Nitrates (symptomatic control, no clear impact on survival)  
  ▪ decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion  
  ▪ maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)

5. Calcium channel blockers (CCBs, second-line or combination)  
  ▪ increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)  
  ▪ caution: verapamil/diltiazem combined with β-blockers may cause symptomatic sinus bradycardia or AV block

6. ACE inhibitors (ACEI, not used to treat symptomatic angina)  
  ▪ angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. HTN, DM, proteinuric renal disease, previous MI with LV dysfunction)  
  ▪ benefit in all patients at high risk for CV disease (concomitant DM, renal dysfunction, or LV systolic dysfunction)  
  ▪ angiotensin II receptor blockers (ARBs) can be used when ACEI contraindicated (e.g. hypersensitivity, angioedema)

7. Invasive strategies  
  ▪ revascularization (see Coronary Revascularization, C31 and COURAGE trial sidebar)

VARIANT ANGINA (Prinzmetal’s Angina)  
• myocardial ischemia secondary to coronary artery vasospasm, with or without atherosclerosis  
• uncommonly associated with infarction or LV dysfunction  
• typically occurs between midnight and 8 AM, unrelated to exercise, relieved by nitrates  
• typically ST elevation on ECG  
• diagnosed by provocative testing with ergot vasoconstrictors (rarely done)  
• treat with nitrates and CCBs

SYNDROME X  
• typical symptoms of angina but normal angiogram  
• may show definite signs of ischemia with exercise testing  
• thought to be due to inadequate vasodilator reserve of coronary resistance vessels  
• better prognosis than overt epicardial atherosclerosis

Canadian Cardiovascular Society (CCS) Functional Classification of Angina  
• Class I: ordinary physical activity (walking, climbing stairs) does not cause angina; angina with strenuous, rapid, or prolonged activity  
• Class II: slight limitation of ordinary activity; angina brought on at >2 blocks on level or climbing >1 flight of stairs or by emotional stress  
• Class III: marked limitation of ordinary activity: angina brought on at <2 blocks on level or climbing <1 flight of stairs  
• Class IV: inability to carry out any physical activity without discomfort; angina may be present at rest

Optimal Medical Therapy With or Without PCI for Stable Coronary Disease. COURAGE Trial NEJM 2007;356:1503-1516  
Study: Randomized, controlled trial with median follow-up of 4.6 yr.  
Population: 2,287 patients who had objective evidence of myocardial ischemia and significant stable coronary artery disease.  
Intervention: Patients were randomized to receive intensive pharmacologic therapy and lifestyle intervention with or without percutaneous coronary intervention (PCI).  
Outcome: Primary outcome was all-cause mortality and nonfatal myocardial infarction (MI). Secondary outcome had additional events of stroke, all MI, and hospitalization for unstable angina with negative biomarkers.  
Results: There was no significant difference in primary (unadjusted hazard ratio: 1.05, p=0.62) or secondary outcomes (hazard ratio: 1.05, p=0.62) between the PCI and non-PCI intervention groups. The PCI group had significantly lower rates of subsequent revascularization at 4.6 yr of follow-up (hazard ratio 0.60, p<0.001) and was more angina-free in the first 4 yr of follow-up.  
Conclusions: PCI as an adjunct in initial management in patients with significant stable coronary artery disease does not reduce mortality, MI, stroke, or hospitalization for ACS, but does provide angina relief and reduced risk of revascularization.
Acute Coronary Syndromes

Definition
- ACS includes the spectrum of UA, NSTEMI, and STEMI; this distinction aids in providing the appropriate therapeutic intervention
- MI is defined by evidence of myocardial necrosis. It is diagnosed by a rise/fall of serum markers plus any one of:
  - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
  - ECG changes (ST-T changes, new BBB or pathological Q waves)
  - imaging evidence (myocardial loss of viability, wall motion abnormality, or intracoronary thrombus)
- if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
- NSTEMI meets criteria for myocardial infarction without ST elevation or BBB
- STEMI meets criteria for myocardial infarction characterized by ST elevation or new BBB
- UA is clinically defined by any of the following:
  - accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion, decreased response to treatment
  - angina at rest
  - new-onset angina
  - angina post-MI or post-procedure (e.g. percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG])

Investigations
- history and physical
  - note that up to 30% of MIs are unrecognized or “silent” due to atypical symptoms – more common in women, DM, elderly, post-heart transplant (because of denervation)
- ECG
- CXR
- labs
  - serum cardiac biomarkers for myocardial damage (repeat 8 h later) (see Cardiac Biomarkers, C11)
  - CBC, INR/PTT, electrolytes and magnesium, creatinine, urea, glucose, serum lipids
  - draw serum lipids within 24-48 h because values are unreliable from 2-48 d post-MI

MANAGEMENT OF ACUTE CORONARY SYNDROMES

1. General measures
   - ABCs: assess and correct hemodynamic status first
   - bed rest, cardiac monitoring, oxygen
   - nitroglycerin SL followed by IV
   - morphine IV

2. Anti-platelet and anticoagulation therapy
   - ASA (81mg) chewed
   - NSTEMI
     - ticagrelor in addition to ASA or if ASA contraindicated, subcutaneous low molecular weight heparin or IV unfractionated heparin (UFH) (LMWH preferable, except in renal failure or if CABG is planned within 24 h)
     - clopidogrel used if patient ineligible for ticagrelor and prasugrel
     - prasugrel contraindicated in those with a history of stroke/TIA, and avoidance of or lower dose is recommended for those >75 yr old or weighing <60 kg (TRITON-TIMI 38)
   - anticoagulation options depend on reperfusion strategy
     - primary PCI: UFH during procedure; bivalirudin is a possible alternative
     - thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
     - no reperfusion: LMWH (enoxaparin) until discharge from hospital
     - continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)

3. β-blockers
   - first dose IV followed by oral administration
   - STEMI: contraindications include signs of heart failure, low output states, risk of cardiogenic shock, heart block, asthma or airway disease; initiate orally within 24 h of diagnosis when indicated
if β-blockers are contraindicated or if β-blockers/nitrates fail to relieve ischemia, non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (calcium channel blockers do not prevent MI or decrease mortality)

4. Invasive strategies and reperfusion options

- UA/NSTEMI: early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  - recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  - CHF or LV dysfunction
  - hemodynamic instability
  - high (≥3) TIMI risk score (tool used to estimate mortality following an ACS)
  - sustained ventricular tachycardia
  - dynamic ECG changes
  - high-risk findings on non-invasive stress testing
  - PCI within the previous 6 mo
  - repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high risk features
  - note: thrombolyis is NOT administered for UA/NSTEMI

- STEMI
  - after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - goal is to re-perfuse artery: thrombolysis ("EMS-to-needle") within 30 min or primary PCI ("EMS-to-balloon") within 90 min (depending on capabilities of hospital and access with PCI facility)
  - thrombolysis
    - preferred if patient presents ≤12 h of symptom onset, and <30 min after presentation to hospital, has contraindications to PCI, or PCI cannot be administered within 90 min
  - PCI
    - early PCI (≤12 h after symptom onset and <90 min after presentation) improves mortality vs. thrombolysis with fewer intra-cranial hemorrhages and recurrent MIs
    - rescue PCI: following failed thrombolytic therapy (diagnosed when following thrombolysis, ST segment elevation fails to resolve below half its initial magnitude and patient still having chest pain)

Figure 35. Reperfusion strategy in STEMI

Table 8. Contraindications for Thrombolysis in STEMI

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior intracranial hemorrhage</td>
<td>Chronic, severe, poorly controlled HTN</td>
</tr>
<tr>
<td>Known structural cerebral vascular lesion</td>
<td>Uncontrolled HTN (SBP &gt; 180, DBP &gt; 110)</td>
</tr>
<tr>
<td>Known malignant intracranial neoplasm</td>
<td>Current anticoagulation</td>
</tr>
<tr>
<td>Significant closed-head or facial trauma (≤3 mo)</td>
<td>Noncompressible vascular punctures</td>
</tr>
<tr>
<td>Ischemic stroke (≤3 mo)</td>
<td>Ischemic stroke (≤3 mo)</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>Recent internal bleeding (≤2-4 wk)</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
<td>Prolonged CPR or major surgery (≤3 wk)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Active peptic ulcer disease</td>
</tr>
</tbody>
</table>

Enoxaparin vs. Unfractionated Heparin with Fibrinolysis for ST-Elevation Myocardial Infarction

Study: Prospective multicenter RCT.

Patients: 20,479 patients (median age 60 yr. 77% male) with STEMI who were scheduled to undergo thrombolysis.

Intervention: Patients were randomized to receive either enoxaparin or weight based unfractionated heparin in addition to thrombolysis and standard therapies.

Primary Outcome: Death or recurrent nonfatal MI 30 d post-event.

Results: The composite primary outcome occurred less often in the enoxaparin group compared with those who received unfractionated heparin (9.9% vs. 12.0%, p = 0.001, NNT = 47). Taken separately, there was a trend toward reduced mortality (6.9% vs. 7.5%, p = 0.11) and a significant reduction in nonfatal reinfarction (3.0% vs. 4.5%, p < 0.001) in the enoxaparin group. The risk of major bleeding was significantly increased in the enoxaparin group (2.1% vs. 1.4%, p < 0.001, NNH = 142).

Conclusion: In patients with STEMI receiving thrombolysis, enoxaparin is superior to unfractionated heparin in preventing recurrent nonfatal MI and may lead to a small reduction in mortality.
Long-Term Management of ACS

- risk of progression to MI or recurrence of MI or death is highest within 1 mo
- at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- pre-discharge workup: ECG and echo to assess residual LV systolic function
- drugs required in hospital to control ischemia should be continued after discharge in all patients
- other medications for long-term management of ACS are summarized below

1. General Measures
   - education
   - risk factor modification

2. Antiplatelet and Anticoagulation Therapy
   - EÇASA 81 mg daily
   - ticagrelor 90 mg twice daily or prasugrel 10 mg daily (at least 1 mo, up to 9-12 mo, if stent placed at least 12 mo)
   - clopidogrel 75 mg daily can be used as alternatives to ticagrelor and prasugrel when indicated
   - ± warfarin x 3 mo if high risk (large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)

3. β-Blockers (e.g. metoprolol 25-50 mg bid or atenolol 50-100 mg daily)

4. Nitrates
   - alleviate ischemia but do not improve outcome
   - use with caution in right-sided MI patients who have become preload dependent

5. Calcium Channel Blockers (NOT recommended as first line treatment, consider as alternative to β-blockers)

6. Angiotensin-Converting Enzyme Inhibitors
   - prevent adverse ventricular remodelling
   - recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
   - recommended for symptomatic CHF, reduced LVEF (<40%), anterior MI
   - use ARBs in patients who are intolerant of ACEI

7. ± Aldosterone Antagonists
   - if on ACEI and β-blockers and LVEF <40% and CHF or DM
   - significant mortality benefit shown with eplerenone by 30 d

8. Statins (early, intensive, irrespective of cholesterol level; e.g. atorvastatin 80 mg daily)

9. Invasive Cardiac Catheterization if indicated (risk stratification)

Post-Infarction Risk Stratification

High Risk (30-35%)
- Prior MI
- CHF
- Recurrent Ischemia
- High-Risk Arrhythmia

Intermediate/Low-Risk (65-70%)

Non-Invasive Stress Testing

Ischemia or Poor Functional Status

Cardiac Catheterization

*note: echo done routinely post-MI

Figure 36. Post-MI risk stratification

Prognosis following STEMI

- 5-15% of hospitalized patients will die
- risk factors
  - infarct size/severity
  - age
  - comorbid conditions
  - development of heart failure or hypotension
- post-discharge mortality rates
  - 6-8% within first year, half of these within first 3 mo
  - 4% per year following first yr
- risk factors
  - LV dysfunction
  - residual myocardial ischemia
  - ventricular arrhythmias
  - history of prior MI

Intensive vs. Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

**Study:** Prospective, double blind, RCT; mean follow-up of 2 yr.
**Population:** 4,162 patients who had been hospitalized for an ACS within the preceding 10 d.
**Intervention:** Patients were randomized to receiving pravastatin 40 mg or atorvastatin 80 mg daily.
**Primary Outcome:** Composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 d after randomization), and stroke.
**Results:** High dose atorvastatin was associated with a 16% hazard ratio reduction (p=0.005; 95% CI 5-26%) in the primary outcome compared to standard dose pravastatin.
**Conclusions:** In patients who recently experienced an ACS, high dose statin therapy provides greater protection against death and major cardiovascular events than standard dose therapy.
Table 9. Complications of Myocardial Infarction

<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology</th>
<th>Presentation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td>Sinus, AFib, VT, VFib, Sinus, AV block</td>
<td>First 48 h</td>
<td>See Arrhythmias, C15</td>
</tr>
<tr>
<td>Myocardial Rupture</td>
<td>Transmural infarction, Inferior infarction, Septal infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td></td>
<td>Transmural infarction, Inferior infarction, Septal infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>Shock/CHF</td>
<td>Infarct or aneurysm</td>
<td>Within 48 h</td>
<td>Inotropes, intra-aortic balloon pump</td>
</tr>
<tr>
<td>Post-Infarct Angina</td>
<td>Persistent coronary stenosis, Multivessel disease</td>
<td>Anytime</td>
<td>Aggressive medical therapy, PCI or CABG</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>Recurrence</td>
<td>Anytime</td>
<td>Aggressive medical therapy, PCI or CABG</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>Mural/apical thrombus, DVT</td>
<td>7-10 d, up to 6 mo</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Inflammatory</td>
<td>1-7 d</td>
<td>ASA</td>
</tr>
<tr>
<td>Dressler’s Syndrome</td>
<td>Autoimmune</td>
<td>2-8 wk</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Algorithm for Chest Pain

1. 12-lead electrocardiogram
2. Aspirin
3. Supplemental oxygen
4. Sublingual nitroglycerin
5. Morphine PRN
6. Cardiac enzymes

Symptoms suggestive of an acute coronary syndrome

No ST-segment changes, initial enzymes normal

Observe:
1. Nitroglycerin PRN
2. Analgesia
3. Serial ECG and cardiac enzymes

No current chest pain, serial studies negative

Provocative stress testing

Negative results

Provocative stress testing

Positive results

Search for other causes of chest pain

High-risk markers present
1. Elevated troponin
2. Persistent/recurrent chest pain
3. Persistent ST depression
4. Associated heart failure
5. Hemodynamic instability
6. LV EF < 40%
7. PCI in preceding 6 months

No high-risk markers

Positive results

1. Clopidogrel
2. LMWH

ST-segment elevation consistent with STEMI

1. IV nitroglycerin
2. Heparin
3. IV β-blocker

1º PCI not available

1º PCI available

Thrombolytic therapy

Primary PCI

Predischarge stress testing

Positive results

Aggressive risk factor modification

Long-term anti-anginal therapy

ECG = electrocardiogram; LMWH = low-molecular-weight heparin; NSTEMI = non-ST-segment elevation myocardial infarction;
PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction

Elevated troponin

Figure 37. Treatment algorithm for patients with symptoms suggestive of an acute coronary syndrome

**Sudden Cardiac Arrest**

**Definition**
- unanticipated, non-traumatic cardiac death in a stable patient which occurs within 1 h of symptom onset; VFib is most common cause

**Etiology**
- primary cardiac pathology
  - ischemia/MI
  - LV dysfunction
  - severe ventricular hypertrophy
    - HCM
    - AS
  - long QT syndrome
  - congenital heart disease
  - mutations in cardiac ion channels

**Management**
- acute: resuscitate with prompt CPR and defibrillation
- investigate underlying cause (cardiac catheterization, electrophysiologic studies, echo)
- treat underlying cause
- antiarrhythmic drug therapy: amiodarone, β-blockers
- implantable cardioverter defibrillator (ICD)
- refer to ACLS guidelines (see Anesthesia, A32)

**Coronary Revascularization**

**PERCUTANEOUS CORONARY INTERVENTION**
- interventional cardiology technique aimed at relieving significant coronary stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

**Balloon Angioplasty and Intracoronary Stenting**
- coronary lesions dilated with balloon inflation
- major complication is restenosis (approximately 15% at 6 mo), felt to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
  - bare metal stent (BMS)
  - drug-eluting stent (DES)
    - coated with antiproliferative drugs (sirolimus, paclitaxel)
    - reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
    - complication: late stent thrombosis (5 events per 1,000 stents implanted)

**Adjunctive Therapies**
- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, epifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
  - dual antiplatelet therapy (ASA and clopidogrel) for 1 mo with BMS or ≥12 mo with DES
  - ASA and prasugrel can be considered for those at increased risk of stent thrombosis

**Procedural Complications**
- mortality and emergency bypass rates <1%
- nonfatal MI: approximately 2-3%

**CORONARY ARTERY BYPASS GRAFT SURGERY**
- objective of CABG is complete reperfusion of the myocardium

**Indications**
- CABG
  - ≥50% diameter stenosis in the left main coronary artery
  - ≥70% diameter stenosis in three major coronary arteries
  - ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
- Survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery
- Other
  - ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
  - ≥70% diameter stenosis in the proximal LAD artery and evidence of extensive ischemia
  - Multivessel CAD in patients with diabetes
  - LV systolic dysfunction (LVEF 35-50%) and significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization
- PCI
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG
- CABG or PCI
  - One or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

### Table 10. Choice of Revascularization Procedure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Advantages</th>
<th>Indications</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI</td>
<td>Less invasive technique</td>
<td>Single or double-vessel disease</td>
<td>DM, Plaque morphology unfavorable for PCI</td>
</tr>
<tr>
<td></td>
<td>Decreased periprocedural morbidity and mortality</td>
<td>Inability to tolerate surgery</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>Greater ability to achieve complete revascularization</td>
<td>Triple-vessel or left main disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased need for repeated revascularization procedures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 11. Conduits for CABG

<table>
<thead>
<tr>
<th>Graft</th>
<th>Occlusion/Patency Rate</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saphenous Vein (SVG)</td>
<td>At 10 yr, 50% occluded,</td>
<td>Used when arterial grafts are not available or many grafts</td>
</tr>
<tr>
<td>Grafts (SVG)</td>
<td>25% stenotic, 25% angiographically normal</td>
<td>are required, such as triple or quadruple bypass</td>
</tr>
<tr>
<td>Left Internal Thoracic/Mammary Artery (LITA/LIMA) (LIMA to LAD)</td>
<td>90-95% patency at 15 yr</td>
<td>Most preferred option because of excellent patency</td>
</tr>
<tr>
<td>Right Internal Thoracic/Mammary Artery (RTA/RIMA)</td>
<td>Pedicled RIMA patency comparable to LIMA</td>
<td>Used in bilateral ITA/IMA grafting</td>
</tr>
<tr>
<td>Radial Artery (free graft)</td>
<td>85-90% patency at 5 yr</td>
<td>Prone to severe vasospasm post-operatively due to muscular wall</td>
</tr>
<tr>
<td>Right Gastroepiploic Artery</td>
<td>80-90% patency at 5 yr</td>
<td>Primarily used as an in situ graft to bypass the RCA</td>
</tr>
</tbody>
</table>

### Operative Issues
- Left ventricular (LV) function is an important determinant of outcome of all heart diseases
- Patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- Assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, PET scanning, or MRI

### CABG and Antiplatelet Regimens
- Please refer to 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery for more information
- Prior to CABG, clopidogrel and ticagrelor should be discontinued for 5 d and prasugrel for 7 d before surgery
- Dual antiplatelet therapy should be continued for 12 mo in patients with ACS within 48-72 h after CABG
- ASA (81mg) continued indefinitely (can be started 6 h after surgery)
- Patients requiring CABG after PCI should continue their dual antiplatelet therapy as recommended in the post-PCI guidelines
heart failure: a complex clinical syndrome, resulting from almost any cardiac disorder that impairs the ability of the ventricle to fill with or eject blood
• backward heart failure: heart unable to accommodate venous return resulting in elevated filling pressures and vascular congestion (systemic or pulmonary)
• heart failure can involve left side of heart (left heart failure), right side (right heart failure), or both (biventricular failure) (see Table 13)
• heart failure can also have components of ineffective ventricular filling (diastolic dysfunction) and/or contraction (systolic dysfunction)
• most cases associated with poor cardiac output (low-output heart failure); however, some cases of CHF not due to intrinsic cardiac disease but instead due to increased demand (high-output heart failure)

Table 12. Risk Factors for CABG Mortality and Morbidity (decreasing order of significance)

<table>
<thead>
<tr>
<th>Risk Factors for CABG Mortality</th>
<th>Risk Factors for CABG Post-Operative Morbidity or Increased Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency of surgery (emergent or urgent)</td>
<td>Reoperation</td>
</tr>
<tr>
<td>Reoperation</td>
<td>Emergent procedure</td>
</tr>
<tr>
<td>Older age</td>
<td>Pre-operative intra-aortic balloon pump (IABP)</td>
</tr>
<tr>
<td>Poor left ventricular function (see below)</td>
<td>CHF</td>
</tr>
<tr>
<td>Female gender</td>
<td>CABG + valve surgery</td>
</tr>
<tr>
<td>Left main disease</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR, dialysis-dependent renal failure, end-stage COPD, DM, cerebrovascular disease, and peripheral vascular disease)</td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
</tbody>
</table>

Procedural Complications
• CABG using cardiopulmonary bypass (CPB)
  • stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
  • immunosuppression
  • systemic inflammatory response leading to:
    • myocardial dysfunction
    • renal dysfunction
    • neurological injury
    • respiratory dysfunction
  • coagulopathies

OFF-PUMP CORONARY ARTERY BYPASS SURGERY

Procedure
• avoids the use of CPB by allowing surgeons to operate on a beating heart
  • stabilization devices (e.g. Genzyme Immobilizer®) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
• procedure is safe and well tolerated by most patients; however, this surgery remains technically more demanding

Indications
• used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe peripheral vascular disease (PVD), severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g. Jehovah’s Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
• absolute contraindications: hemodynamic instability, poor quality target vessels including intramycocardial vessels, diffusely diseased vessels, and calcified coronary vessels
• relative contraindications: cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

Outcomes
• OPCAB decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
• no significant difference in terms of survival at 2 yr, frequency of cardiac events (MI, PCI, CHF, recurrent angina, redo CABG), or medication usage compared to on-pump CABG
Pathophysiology

- primary insults (myocyte loss, overload) → pump dysfunction, which leads to:
  - remodeling (dilatation, hypertrophy)
  - neurohumoral activation → necrosis and apoptosis
- both pathways result in further damage (re-starting the cycle), edema, tachycardia, pump dysfunction, which leads to:
  - primary insults (myocyte loss, overload)
- systemic response to ineffective circulating volume

Systolic Dysfunction

- impaired myocardial contractile function → decreased LVEF and SV → decreased CO
- findings: apex beat displaced, S3, increased heart size on CXR, decreased LVEF, LV dilatation
- causes
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - alcohol (and other toxins)
    - myocarditis
    - dilated cardiomyopathy (multiple causes – see Dilated Cardiomyopathy, C39)

Heart Failure with Preserved Ejection Fraction

- previously known as ‘diastolic dysfunction’
- up to 1/2 of all HF patients have normal systolic function (i.e. normal ejection fraction) and the cause of heart failure is impaired diastolic filling: prevalence higher in older patients
- increased LV filling pressures produce venous congestion upstream (i.e. pulmonary and systemic venous congestion)
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, LVH on ECG/echo, normal LVEF
- causes of decreased compliance:
  - transient: ischemia (relaxation of myocardium is active and requires ATP)
  - permanent
    - severe hypertrophy (HTN, aortic stenosis, HCM)
    - restrictive cardiomyopathy (e.g. amyloid)
    - MI

High-Output Heart Failure

- caused by demand for increased cardiac output
- often exacerbates existing heart failure or decompensates a patient with other cardiac pathology
- differential diagnosis: anemia, thiamine deficiency (beriberi), hyperthyroidism, A-V fistula or L-R shunting, Paget’s disease, renal disease, hepatic disease
Etiologies of Primary Insults
- consider predisposing, precipitating, and perpetuating factors

Precipitants of Symptomatic Exacerbations
- consider natural progression of disease vs. new precipitant
- always search for reversible cause
- differential diagnosis can also be organized as follows:
  - new cardiac insult/disease: MI, arrhythmia, valvular disease
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection, etc.
  - failure to take medications as prescribed

Investigations
- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), BUN, creatinine, fasting blood glucose, HbA1c, lipid profile, liver function tests, serum TSH, ± ferritin, BNP, uric acid
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchiolar-alveolar cuffing
- echo: LVEF, cardiac dimensions, wall motion abnormalities, valvular disease, pericardial effusion
- radionuclide angiography: LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)

Acute Treatment of Pulmonary Edema
- treat acute precipitating factors (e.g. ischemia, arrhythmias)
- L = Lasix® (furosemide) 40-500 mg IV
- M = morphine 2-4 mg IV: decreases anxiety and preload (venodilation)
- N = nitroglycerin: topical/IV/SL
- O = oxygen: in hypoxemic patients
- P = positive airway pressure (CPAP/BiPAP): decreases preload and need for ventilation when appropriate
- P = position: sit patient up with legs hanging down unless patient is hypotensive
- in ICU setting or failure of LMNOPP, other interventions may be necessary
  - dopamine
    - low dose: selective renal vasodilation (high potency D1 agonist)
    - medium dose: inotropic support (medium potency β1 agonist)
    - high dose: increases SVR (low potency β1 agonist), which is undesirable
  - dobutamine
    - selective inotropic (β1 agonist) and arterial vasodilator (β1 antagonist)
  - phosphodiesterase inhibitors (milrinone)
    - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
  - consider pulmonary artery catheter to monitor pulmonary capillary wedge pressure (PCWP)
  - if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac failure)
  - mechanical ventilation as needed
  - rarely used, but potentially life-saving measures:
    - intra-aortic balloon pump (IABP)
    - left or right ventricular assist device (LVAD/RVAD)
    - cardiac transplant

Long-Term Management
- note that most evidence-based management applies to HFPEF
- priorities in HFPEF focus on controlling systolic and diastolic HTN, as a risk factor control measure

Conservative Measures
- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease alcohol consumption, patient education, sodium and fluid restriction
- multidisciplinary heart failure clinics: for management of individuals at higher risk, or with recent hospitalization
Non-Pharmacological Management
• cardiac rehabilitation: participation in a structured exercise program for NYHA class I-III after clinical status assessment to improve quality of life (HF-ACTION trial)

Pharmacological Therapy

1. Vasodilators
   • ACEI: standard of care – slows progression of LV dysfunction and improves survival
     • all symptomatic patients functional class II-IV
     • all asymptomatic patients with LVEF <40%
     • post-MI
     • angiotensin II receptor blockers
       • second-line to ACEI if not tolerated, or as adjunct to ACEI if β-blockers not tolerated
       – hydralazine and nitrates
     • second-line to ACEI, decrease in mortality not as great as with ACEI
     • may consider in acute renal failure until creatinine stabilizes

2. β-blockers: slow progression and improve survival
   • class I-III with LVEF <40%
   • stable class IV patients
   • note: should be used cautiously, titrate slowly because may initially worsen CHF

3. Diuretics: symptom control, management of fluid overload
   • furosemide (40-500 mg daily) for potent diuresis
   • metolazone may be used with furosemide to increase diuresis
   • furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by β-blockers, ACEI, ARBs, and aldosterone antagonists

4. Mineralocorticoid receptor (aldosterone) antagonists: mortality benefit in symptomatic heart failure and severely depressed ejection fraction
   • spironolactone for class IIIb and IV CHF already on ACEI and loop diuretic
   • eplerenone may be considered if intolerable endocrine side effects
   • note: potential for life threatening hyperkalemia
     • monitor K+ after initiation and avoid if Cr >2.9 mg/dL or K+ >5.2 mEq/L

5. Digoxin and cardiac glycosides: digoxin improves symptoms and decreases hospitalizations, no effect on mortality
   • indications: patient in sinus rhythm and symptomatic on ACEI, or CHF and AFib
   • patients on digitals glycosides may worsen if these are withdrawn

6. Antiarrhythmic drugs: for use in CHF with arrhythmia
   • can use amiodarone, β-blocker, or digoxin

7. Anticoagulants: warfarin for prevention of thromboemolic events
   • prior thromboembolic event or AFib, presence of LV thrombus on echo
   • possible benefit in other patients with LVEF <30% (controversial)

Procedural Interventions
• resynchronization therapy: symptomatic improvement with biventricular pacemaker
  • consider if QRS >130 msec, LVEF <35%, and severe symptoms despite optimal therapy
  • greatest benefit likely with marked LV enlargement, mitral regurgitation, QRS >150 msec, high diuretic requirement
• ICD: mortality benefit in 1st prevention of sudden cardiac death
  • prior MI, optimal medical therapy, LVEF <30%, clinically stable
  • prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
• LVAD/RVAD (see Ventricular Assist Devices, C38)
• cardiac transplantation (see Cardiac Transplantation, C37)
• valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see Valvular Heart Disease, C41)
Sleep-Disordered Breathing

- 45-55% of patients with CHF have sleep disturbances, including Cheyne-Stokes breathing and sleep apnea (central or obstructive)
- associated with a worse prognosis and greater LV dysfunction
- nasal continuous positive airway pressure (CPAP) is effective in treating symptoms of sleep apnea with secondary beneficial effects in cardiac function and symptoms

Cardiac Transplantation

- treatment for end-stage heart disease; due to ischemic or non-ischemic cardiomyopathy
- worldwide 1 yr survival is 85-90%, 5 yr survival about 60%, annual mortality rate of 4%
- matching is according to blood type, body size and weight (should be within 25%), and HLA tissue matching (if time allows)

Indications for Surgery

- severe cardiac disability despite maximal medical therapy (recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 mL/kg/min in absence of β-blocker)
- symptomatic cardiac ischemia refractory to conventional treatment (unstable angina not amenable to CABG or PCI with LVEF <30%; recurrent, symptomatic ventricular arrhythmias)
- exclusion of all surgical alternatives to cardiac transplantation

Prerequisites

- emotionally stable with social support
- medically compliant and motivated
- relative contraindications: incurable malignancy, major systemic illness, irreversible major organ disease, active systemic infection (e.g. hepatitis C, HIV), obesity, irreversible pulmonary HTN (pulmonary vascular resistance [PVR] >6 Wood units), severe COPD (FEV₁ <1 L) or active drug addiction or alcoholism

Complications

- rejection
  - common, <5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
  - no noninvasive tests to detect rejection
  - risk of acute rejection is greatest during the first 3 mo after transplant
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
  - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft CAD
  - approximately 50% develop graft CAD within 5 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
second most common cause of late death following transplantation
• cutaneous neoplasms most common, followed by non-Hodgkin's lymphoma and lung cancer
• immunosuppressive medication side effects (prednisone, cyclosporine, tacrolimus, sirolimus)

**Ventricular Assist Devices**

• work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
• can support the left (LVAD), right (RVAD), or both ventricles (BiVAD)
• indications
  • bridge to transplantation
  • post-operative mechanical support when unable to separate from cardiopulmonary bypass despite inotropic and intra-aortic balloon pump (IABP) support
    • IABP is a catheter based device inserted into the aorta via the femoral artery that decreases myocardial O₂ demand and increases blood flow to coronary arteries
  • post-operative cardiogenic shock

**Myocardial Disease**

**Definition of Cardiomyopathy**

• intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
• functional classification: dilated, hypertrophic, or restrictive
• LV dysfunction 2º to MI often termed “ischemic cardiomyopathy”, is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD

<table>
<thead>
<tr>
<th>SYSTOLIC HEART FAILURE</th>
<th>DIASTOLIC HEART FAILURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated Cardiomyopathy</td>
<td>Secondary Causes</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic Cardiomyopathy</td>
</tr>
<tr>
<td>Idiopathic, infectious (e.g. myocarditis), alcohol, familial, collagen vascular disease, etc.</td>
<td>CAD, MI, DM, valvular (e.g. AR, MR)</td>
</tr>
<tr>
<td></td>
<td>Secondary Causes</td>
</tr>
<tr>
<td></td>
<td>HTN, DM, valvular (e.g. AS), post-MI, transiently by ischemia, etc.</td>
</tr>
</tbody>
</table>

**Myocarditis**

**Definition**

• inflammatory process involving the myocardium ranging from acute to chronic; an important cause of dilated cardiomyopathy

**Etiology**

• idiopathic
• infectious
  • viral (most common): parvovirus B19, influenza, coxsackie B, echovirus, poliovirus, HIV, mumps
  • bacterial: *S. aureus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia*
  • fungi
  • spirochetal (Lyme disease – *Borrelia burgdorferi*)
  • Chagas disease (*Trypanosoma cruzi*), toxoplasmosis
• toxic: catecholamines, chemotherapy, cocaine
• hypersensitivity/cosinophilic: drugs (antibiotics, diuretics, lithium, clozapine), insect/snake bites
• systemic diseases: collagen vascular diseases (SLE, rheumatoid arthritis, others), sarcoidosis, autoimmune
• other: giant cell myocarditis, acute rheumatic fever

**Signs and Symptoms**

• constitutional symptoms
• acute CHF
• chest pain – due to pericarditis or cardiac ischemia
• arrhythmias
• systemic or pulmonary emboli
• sudden death

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**REMATCH Trial**

*NEJM* 2001;345:1435-1443

Increased survival of 23% vs. 8% with LVAD vs. medical management of heart failure after 2 yr. Heartmate VAD has a biologic surface therefore does not require long-term anticoagulation but higher risk of infection.
Investigations
- ECG: non-specific ST-T changes ± conduction defects
- blood work
  - increased CK, troponin, LDH, and AST with acute myocardial necrosis ± increased WBC, ESR, ANA, rheumatoid factor, complement levels
  - blood culture, viral titres and cold agglutinins for Mycoplasma
- CXR: enlarged cardiac silhouette
- echo: dilated, hypokinetic chambers, segmental wall motion abnormalities
- cardiovascular magnetic resonance: functional and morphological abnormalities as well as tissue pathology (gadolinium enhancement)
- myocardial biopsy

Management
- supportive care
- restrict physical activity
- treat CHF
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible

Prognosis
- usually self-limited and often unrecognized, many recover
- sudden death in young adults
- may progress to dilated cardiomyopathy

Dilated Cardiomyopathy

Definition
- unexplained dilation and impaired systolic function of one or both ventricles

Etiology
- idiopathic (presumed viral or idiopathic) ~50% of DCM
- alcohol
- familial/genetic
- uncontrolled tachycardia (e.g. persistent rapid AFib)
- collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
- infectious: viral (coxsackie B, HIV), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
- neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
- metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
- endocrine: hyper/hypothyroidism, DM, pheochromocytoma
- peripartum
- toxic: cocaine, heroin, organic solvents
- drugs: chemotherapies (doxorubicin, cyclophosphamide), antiretrovirals, chloroquine, clozapine, TCA
- radiation

Signs and Symptoms
- may present as
  - CHF
  - systemic or pulmonary emboli
  - arrhythmias
  - sudden death (major cause of mortality due to fatal arrhythmia)

Investigations
- blood work: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, TIBC
- ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (non-sustained VT)
- CXR: global cardiomegaly (globular heart), signs of CHF, pleural effusion
- echo: chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi
- endomyocardial biopsy: not routine, used to rule out a treatable cause
- coronary angiography: in selected patients to exclude ischemic heart disease

Management
- treat underlying disease: e.g. abstinence from alcohol
- treat CHF: see Heart Failure, C33
- thromboembolism prophylaxis: anticoagulation with warfarin
  - indicated for: AFib, history of thromboembolism or documented thrombus
  - LVEF <30% (controversial)
- treat symptomatic or serious arrhythmias
- immunize against influenza and S. pneumoniae
- consider surgical options (e.g. LVAD, transplant, volume reduction surgery) in appropriate candidates with severe, drug refractory disease
- consider ICD among patients with a LVEF <30%
Prognosis
• depends on etiology
• better with reversible underlying cause, worst with infiltrative diseases, HIV, drug-induced
• cause of death usually CHF (due to pump failure) or sudden death 2° to ventricular arrhythmias
• systemic emboli are significant source of morbidity
• 20% mortality in 1st yr, 10% per year after

Hypertrophic Cardiomyopathy

Definition
• defined as unexplained ventricular hypertrophy
• various patterns of HCM are classified, but most causes involve pattern of septal hypertrophy

Etiology and Pathophysiology
• histopathologic features include myocyte disarray, myocyte hypertrophy, and interstitial fibrosis
• cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins (>400 mutations associated with autosomal dominant inheritance, incomplete penetrance)
• prevalence of 1/500-1/1,000 in general population
• generally presents in early adulthood

Hemodynamic Classification
• hypertrophic obstructive cardiomyopathy (HOCM): dynamic LV outflow tract (LVOT) obstruction, either at rest or with provocation, defined as LVOT gradient of at least 30 mmHg
• non-obstructive HCM: no LVOT obstruction
• many patients have diastolic dysfunction (impaired ventricular filling secondary to LV hypertrophy which decreases compliance)

Signs and Symptoms
• clinical manifestations: asymptomatic (common, therefore screening is important), SOB on exertion, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
• pulses: rapid upstroke, “spike and dome” pattern in carotid pulse (in HCM with outflow tract obstruction)
• precordial palpation: PMI localized, sustained, double impulse, ‘triple ripple’ (triple apical impulse in HOCM), LV lift
• precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LSB or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOT obstruction as compared to AS); often with pansystolic murmur due to mitral regurgitation

Investigations
• ECG/Holter monitor: LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
• transthoracic echocardiography and echo-Doppler study: asymmetric septal hypertrophy (less commonly apical), systolic anterior motion (SAM) of mitral valve and MR; LVOT gradient can be estimated by Doppler measurement
• genetic studies (± magnetic resonance imaging) can be helpful when echocardiography is inconclusive for diagnosis
• cardiac catheterization (only when patient being considered for invasive therapy)

Management
• avoid factors which increase obstruction (e.g. volume depletion)
  ▪ avoidance of all competitive sports
• treatment of obstructive HCM
  ▪ medical agents: β-blockers, disopyramide, verapamil (started only in monitored setting), phenylephrine (in setting of cardiogenic shock)
  ▪ avoid nitrates, diuretics, and ACEI as they increase LVOT gradient and worsen symptoms
• patients with obstructive HCM and drug-refractory symptoms
  ▪ surgical myectomy
  ▪ ICD placement
  ▪ septal ethanol ablation
  ▪ dual chamber pacing (rarely done)
• treatment of ventricular arrhythmias: amiodarone or ICD
• first-degree relatives (children, siblings, parents) of patients with HCM should be screened (physical, ECG, 2D echo) every 12-18 mo during during adolescence, then serially every 5 yr during adulthood
Prognosis
- potential complications: AFib, VT, CHF, sudden cardiac death (1% risk/yr; most common cause of SCD in young athletes)
  - major risk factors for sudden death (consider ICD placement)
  - history of survived cardiac arrest/sustained VT
  - family history of multiple premature sudden deaths
  - other factors associated with increased risk of sudden cardiac death
    - syncope (presumed to be arrhythmic in origin)
    - non-sustained VT on ambulatory monitoring
    - marked ventricular hypertrophy (maximum wall thickness ≥30 mm)
    - abnormal BP in response to exercise (in patients <40 yr old with HCM)

Restrictive Cardiomyopathy

Definition
- impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)

Etiology
- infiltrative: amyloidosis, sarcoidosis
- non-infiltrative: scleroderma, idiopathic myocardial fibrosis
- storage diseases: hemochromatosis, Fabry’s disease, Gaucher’s disease, glycogen storage diseases
- endomyocardial
  - endomyocardial fibrosis, Loeffler’s endocarditis, or eosinophilic endomyocardial disease
  - radiation heart disease
  - carcinoid syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)

Clinical Manifestations
- CHF (usually with preserved LV systolic function), arrhythmias
- elevated JVP with prominent x and y descents, Kussmaul’s sign
- S3, S4, MR, TR
- thromboembolic events

Investigations
- ECG: low voltage, non-specific, diffuse ST-T wave changes ± non-ischemic Q waves
- CXR: mild cardiac enlargement
- echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
- cardiac catheterization: increased end-diastolic ventricular pressures
- endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

Management
- exclude constrictive pericarditis
- treat underlying disease: control HR, anticoagulate if AFib
- supportive care and treatment for CHF, arrhythmias
- heart transplant: might be considered for CHF refractory to medical therapy

Prognosis
- depends on etiology

Valvular Heart Disease

Infective Endocarditis
- see Infectious Diseases, ID17
- American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  - only for patients with
    - prosthetic valve material
    - past history of IE
    - certain types of congenital heart disease
    - cardiac transplant recipients who develop valvulopathy
  - only for the following procedures
    - dental
    - respiratory tract
    - procedures on infected skin/skin structures/MSK structures
    - not GI/GU procedures specifically
Rheumatic Fever

- see Pediatrics, P60

Prognosis

- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease – fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
- onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
- mitral valve most commonly affected

Valve Repair and Valve Replacement

- indication for valve repair or replacement depends on the severity of the pathology; typically recommended when medical management has failed to adequately improve the symptoms or reduce the risk of morbidity and mortality
- pathologies that may require surgical intervention include congenital defects, infections, rheumatic heart disease as well as a variety of valve diseases associated with aging
- valve repair: balloon valvuloplasty, surgical valvuloplasty (commissurotomy, annuloplasty), chordae tendineae shortening, tissue patch
- valve replacement: typically for aortic or mitral valves only; repair is favored in younger individuals; percutaneous techniques being established

Choice of Valve Prosthesis

**Table 15. Mechanical Valve vs. Bioprosthetic Valve**

<table>
<thead>
<tr>
<th>Mechanical Valve</th>
<th>Bioprosthetic Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good durability</td>
<td>Limited long-term durability (mitral &lt; aortic)</td>
</tr>
<tr>
<td>Less preferred in small aortic root sizes</td>
<td>Good flow in small aortic root sizes</td>
</tr>
<tr>
<td>Increased risk of thromboembolism (1-3%/yr): requires long-term anticoagulation with coumadin</td>
<td>Decreased risk of thromboembolism: long-term anticoagulation not needed for aortic valves</td>
</tr>
<tr>
<td>Target INR</td>
<td></td>
</tr>
<tr>
<td>Aortic valves: 2.0-3.0 (mean 2.5)</td>
<td>Some recommendation for limited anticoagulation for mitral valves</td>
</tr>
<tr>
<td>Mitral valves: 2.5-3.5 (mean 3.0)</td>
<td></td>
</tr>
<tr>
<td>Increased risk of hemorrhage: 1-2%/yr</td>
<td>Decreased risk of hemorrhage</td>
</tr>
</tbody>
</table>

A Bedside Clinical Prediction Rule for Detecting Moderate or Severe Aortic Stenosis


**Study Design:** Blinded cross sectional study with 124 patients at an ambulatory cardiology clinic. Patients were examined for: 1) murmur over the right clavicle 2) murmur loudest at second right intercostal space 3) reduced intensity of S2 4) reduced volume of the carotid pulse 5) delayed carotid upstroke.

**Methods:** Patients were examined by blinded investigators and the clinical examination findings were compared to findings on subsequent echocardiography. Moderate to severe aortic stenosis was defined as a valve area <1.2 cm² or a peak intensity gradient of >25 mmHg.

**Results:** Absence of a murmur over the right clavicle ruled out aortic stenosis while presence of ≥3 of the 4 associated symptoms ruled in aortic stenosis (LR+ = 40).

**Conclusions:** Bedside techniques can accurately rule in and rule out moderate to severe aortic stenosis.

Mitral Valve Repair vs. Replacement for Severe Ischemic Mitral Regurgitation

NEJM 2014;370:23-32

**Purpose:** Ischemic mitral regurgitation is associated with significant mortality risk. The purpose of this study was to compare the effectiveness and safety of repairing vs. replacing the mitral valve in patients with severe chronic ischemic mitral regurgitation.

**Study Design:** RCT with 251 patients with severe ischemic mitral regurgitation were randomly assigned to mitral valve repair or chordal-sparing replacement. The primary endpoint was the left ventricular end-systolic volume index (LVESVI) at 12 mo.

**Results:** There were no significant between-group differences in LVESVI, in the rate of major adverse cardiac or cerebrovascular events, in functional status, or in quality of life at 12 mo. The rate of moderate or severe mitral regurgitation recurrence at 12 mo was significantly higher in the repair group than in the replacement group (28.9% vs. 2.3%, respectively).

**Conclusions:** No significant difference in left ventricular reverse remodeling or survival at 12 mo between patients who underwent mitral valve repair or replacement. Replacement provided more durable correction of mitral regurgitation, but there were no significant differences in clinical outcomes.
Table 16. Valvular Heart Disease

Aortic Stenosis (AS)

**Etiology**
Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease

**Definition**
Normal aortic valve area = 3-4 cm²
Mild AS ≤ 1.5 cm²
Moderate AS 1.0 to 1.5 cm²
Severe AS ≤ 1.0 cm²
Critical AS ≤ 0.5 cm²

**Pathophysiology**
Outflow obstruction → increased EDP → concentric LVH → LV failure → CHF
subendocardial ischemia

**Symptoms**
Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema

**Physical Exam**
Narrow pulse pressure, brachial-radial delay, pulsatilis parvus et tardus, sustained PMI
Auscultation: crescendo-decrescendo SEM radiating to R clavicle and carotid, musical quality at apex (Gallavardin phenomenon), S4, soft S2 with paradoxical splitting, S3 (late)

**Investigations**
ECG: LVH and strain, LBBD, LAFib
CXR: post-stenotic aortic root dilatation, calcified valve, LVH, LAE, CHF
Echocardiography: reduced valve area, pressure gradient, LVH, reduced LV function

**Treatment**
Asymptomatic: serial echos, avoid exertion
Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS
Surgery if: symptomatic or LV dysfunction

**Surgical Options**
Valve replacement: aortic valve disease and trileaflet valve
– prior to pregnancy (if AS significant)
– balloon valvuloplasty (in very young)

**Interventional Options**
Percutaneous valve replacement (transfemoral or transapical approach)
is an option in selected patients who are not considered good candidates for surgery

Mitraille Stenosis (MS)

**Etiology**
Rheumatic disease most common cause, congenital (rare)

**Definition**
Severe MS is mitral valve area (MVA) <1.2 cm²

**Pathophysiology**
MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF; worse with Afib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)

**Symptoms**
SGB on exertion, orthopnea, fatigue, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)

**Physical Exam**
Afib, no “a” wave on JVP, left parasternal lift, palpable diastolic thrill at apex
Auscultation: mid-diastolic rumble at apex, best heard with bell in left lateral decubitus position following exertion, loud S1, OS following loud P2 (heard before diastolic murmur), long diastolic murmur and short A2 OS interval correlate with worse MS

**Investigations**
ECG: NSR/Afib, LAE (P mitrale), RVH, RAD
CXR: LAFib, CHF; mitral valve calcification
Echo/TEE: shows restricted opening of mitral valve
Cath: indicated in concurrent CAD if >40 yr (male) or >50 yr (female)

**Treatment**
Avoid exertion, fever (increased LA pressure), treat Afib and CHF, increase diastolic filling time (i-blockers, digitalis)
Surgery if: NYHA class III-IV CHF, LV dilatation/aneurysm (CHF, DCM, myocarditis), IE abscess, Marfan’s syndrome, HOCM, acute MI, myxoma, mtrval valve annulus calcium, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease

**Pathophysiology**
Reduced CO → increased LV and LA pressure → LV and LA dilatation → CHF and pulmonary HTN

**Symptoms**
Dyspnea, PND, orthopnea, palpitations, peripheral edema

**Physical Exam**
Displaced hyperdynamic apex, left parasternal lift, apical thrill
Auscultation: holosystolic murmur at apex, radiating to axilla ± mid-diastolic rumble, loud S2 (if pulmonary HTN), S3

**Investigations**
ECG: LAE, left atrial delay (bifid P waves), ± LVH
CXR: LVH, LAE, pulmonary venous HTN
Echo: etiology and severity of MR, LV function, leaflets
Swan-Ganz Catheter: prominent LA “v” wave

**Treatment**
Asymptomatic: serial echos
Symptomatic: decrease preload (diuretics), decrease afterload (ACEI) for severe MR and poor surgical candidates; stabilize acute MR with vasodilators before surgery
Surgery if: acute MR with CHF, papillary muscle rupture, NYHA class III-IV CHF, AF; increasing LV size or worsening LV function, earlier surgery if valve repairable (> 90% likelihood) and patient is low-risk for surgery

**Surgical Options**
Valve repair: >75% of pts with MR and myxomatous mitral valve prolapse – annuloplasty rings, leaflet repair, chordae transfers/shorten/replacement
Valve replacement: failure of repair, heavily calcified annulus
Advantage of repair: lower rate of endocarditis, no anticoagulation, less chance of re-operation

Aortic Regurgitation (AR)

**Etiology**
Supravalvular: aortic root disease
(Marfan’s, atherosclerosis and dissecting aneurysm, connective tissue disease)
Valvular: congenital (bicuspid aortic valve, large VSD), IE

**Pathophysiology**
Volume overload → LV dilatation → increased SV, high sBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)

**Symptoms**
Usually only becomes symptomatic late in disease when LV failure develops
Dyspnea, orthopnea, PND, syncope, angina

**Physical Exam**
Waterhammer pulse, bisferiens pulse, femoral-brachial sBP >20 (Hill’s test wide pulse pressure), hyperdynamic apex, displaced PMI, heaving apex
Auscultation: early decrescendo diastolic murmur at LLSS (cusp pathology) or RLSB (aortic root pathology), best heard sitting, leaning forward, on full expiration, soft S1, absent S2, S3 (late)

**Investigations**
ECG: LVH, LAE
CXR: LVH, LAE, aortic root dilatation
Echo/TTE: quantify AR, leaflet or aortic root anomalies
Cath: if >40 yr and surgical candidate – to assess for ischemic heart disease

**Exercise Testing**
Hypertension with exercise

**Treatment**
Asymptomatic: serial echos, afterload reduction (e.g. ACEI, nifedipine, hydralazine)
Symptomatic: avoid exertion, treat CHF
Surgery if: NYHA class III-IV CHF; LV dilatation and/or LVF <50% with/without symptoms

**Surgical Options**
Valve replacement: most patients
Valve repair: very limited role

Aortic root replacement (Bentall procedure):
– when ascending aortic aneurysm present, valved conduit used

Mitraille Regurgitation (MR)

**Etiology**
Mitraille valve prolapse, congenital cleft leaflet, LV dilatation/aneurysm (CHF, DCM, myocarditis), IE abscess, Marfan’s syndrome, HOCM, acute MI, myxoma, mtrval valve annulus calcium, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease

**Pathophysiology**
Reduced CO → increased LV and LA pressure → LV and LA dilatation → CHF and pulmonary HTN

**Symptoms**
Dyspnea, PND, orthopnea, palpitations, peripheral edema

**Physical Exam**
Displaced hyperdynamic apex, left parasternal lift, apical thrill
Auscultation: holosystolic murmur at apex, radiating to axilla ± mid-diastolic rumble, loud S2 (if pulmonary HTN), S3

**Investigations**
ECG: LAE, left atrial delay (bifid P waves), ± LVH
CXR: LVH, LAE, pulmonary venous HTN
Echo: etiology and severity of MR, LV function, leaflets
Swan-Ganz Catheter: prominent LA “v” wave

**Treatment**
Asymptomatic: serial echos
Symptomatic: decrease preload (diuretics), decrease afterload (ACEI) for severe MR and poor surgical candidates; stabilize acute MR with vasodilators before surgery
Surgery if: acute MR with CHF, papillary muscle rupture, NYHA class III-IV CHF, AF; increasing LV size or worsening LV function, earlier surgery if valve repairable (> 90% likelihood) and patient is low-risk for surgery

**Surgical Options**
Valve repair: >75% of pts with MR and myxomatous mitral valve prolapse – annuloplasty rings, leaflet repair, chordae transfers/shorten/replacement
Valve replacement: failure of repair, heavily calcified annulus
Advantage of repair: lower rate of endocarditis, no anticoagulation, less chance of re-operation
### Table 16. Valvular Heart Disease (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Etiology</th>
<th>Pathophysiology</th>
<th>Symptoms</th>
<th>Physical Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid Stenosis (TS)</td>
<td>Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS</td>
<td>Increased RV pressure → right heart failure; =&gt; decreased CO and fixed on exertion</td>
<td>Perihypertrophy → right heart failure</td>
<td>ECG: RAE, RVH, AFib; CXR: prominent pulmonary arteries enlarged RV; Echocardiogram: diagnostic</td>
</tr>
<tr>
<td>Tricuspid Regurgitation (TR)</td>
<td>RV dilatation, IE (particularly due to IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid</td>
<td>Pathophysiology: RV dilatation → TR → further RV dilatation → right heart failure</td>
<td>Perihypertrophy; fatigue, peripheral edema; increased wall tension; right heart failure</td>
<td>ECG: RAE, RVH, AFib; CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV; Echocardiogram: diagnostic</td>
</tr>
<tr>
<td>Pulmonary Stenosis (PS)</td>
<td>Usually congenital, rheumatic disease (rare), carcinoid syndrome</td>
<td>Pathophysiology: Increased RV pressure → RV hypertrophy → right heart failure</td>
<td>Chest pain, syncope, fatigue, peripheral edema</td>
<td>ECG: RVH; CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV; Echocardiogram: diagnostic</td>
</tr>
<tr>
<td>Pulmonary Regurgitation (PR)</td>
<td>Pulmonary HTN, IE, rheumatic disease, tetrology of Fallot (post-repair)</td>
<td>Pathophysiology: Increased RV volume → increased wall tension → RV hypertrophy → right heart failure</td>
<td>Chest pain, syncope, fatigue, peripheral edema</td>
<td>ECG: RVH; CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV; Echocardiogram: diagnostic</td>
</tr>
<tr>
<td>Mitral Valve Prolapse (MVP)</td>
<td>Myxomatous degeneration of chordae, thick, bulky leaflets that crowd orifice, associated with Marfan’s syndrome, pectus excavatum, straight back syndrome, other MSK abnormalities; &lt;3% of population</td>
<td>Pathophysiology: Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms</td>
<td>Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope</td>
<td>ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy; Echocardiogram: systolic displacement of thickened mitral valve leaflets into LA; Auscultation: mid-systolic click (due to billowing of mitral leaflet into LA; tensing of redundant valve tissue); midd to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers; Symptomatic: β-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if AFib; Mitral valve surgery (repair favored over replacement) if symptomatic and significant MR</td>
</tr>
</tbody>
</table>

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**Tricuspid Stenosis (TS)**
- **Etiology**: Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS
- **Pathophysiology**: Increased RV pressure → right heart failure → decreased CO and fixed on exertion
- **Symptoms**: Perihypertrophy → right heart failure
- **Physical Exam**: Prominent “a” waves in JVP; +ve abdominojugular reflux, Kussmaul’s sign, diastolic rumble 4th left intercostal space
- **Investigations**: ECG: RAE; CXR: dilatation of RA without pulmonary artery enlargement; Echo: diagnostic
- **Treatment**: Preload reduction (diuretics), slow HR; Surgery: if: only if other surgery required (e.g. mitral valve replacement)
- **Surgical Options**: Valve Replacement:
  - if severely diseased valve
  - bioprosthesis preferred

---

**Pulmonary Stenosis (PS)**
- **Etiology**: Usually congenital, rheumatic disease (rare), carcinoid syndrome
- **Pathophysiology**: Increased RV pressure → RV hypertrophy → right heart failure
- **Symptoms**: Chest pain, syncope, fatigue, peripheral edema
- **Physical Exam**: Systolic murmur at 2nd left intercostal space accentuated by inspiration, pulmonary ejection click, right-sided S4
- **Investigations**: ECG: RVH; CXR: prominent pulmonary arteries enlarged RV; Echocardiogram: diagnostic
- **Treatment**: Balloon valvuloplasty if severe symptoms
- **Surgical Options**: Percutaneous or open balloon valvuloplasty

---

**Tricuspid Regurgitation (TR)**
- **Etiology**: RV dilatation, IE (particularly due to IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid
- **Pathophysiology**: RV dilatation → TR → further RV dilatation → right heart failure
- **Symptoms**: Perihypertrophy; fatigue, peripheral edema
- **Physical Exam**: “c” waves in JVP; +ve abdominojugular reflux, Kussmaul’s sign, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift
- **Investigations**: ECG: RAE, RVH, AFib; CXR: RAE, RV enlargement; Echocardiogram: diagnostic
- **Treatment**: Preload reduction (diuretics); Surgery: if: only if other surgery required (e.g. mitral valve replacement)
- **Surgical Options**: Annuloplasty (i.e. repair, rarely done)

---

**Mitral Valve Prolapse (MVP)**
- **Etiology**: Myxomatous degeneration of chordae, thick, bulky leaflets that crowd orifice, associated with Marfan’s syndrome, pectus excavatum, straight back syndrome, other MSK abnormalities; <3% of population
- **Pathophysiology**: Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms
- **Symptoms**: Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope
- **Physical Exam**: Auscultation: mid-systolic click (due to billowing of mitral leaflet into LA; tensing of redundant valve tissue); mid to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers
- **Investigations**: ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy; Echocardiogram: systolic displacement of thickened mitral valve leaflets into LA
- **Treatment**: Asymptomatic: no treatment; reassurance
- **Symptomatic**: β-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if AFib
- **Surgical Options**: Mitral valve surgery (repair favored over replacement) if symptomatic and significant MR:

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**Pulmonary Regurgitation (PR)**
- **Etiology**: Pulmonary HTN, IE, rheumatic disease, tetrology of Fallot (post-repair)
- **Pathophysiology**: Increased RV volume → increased wall tension → RV hypertrophy → right heart failure
- **Symptoms**: Chest pain, syncope, fatigue, peripheral edema
- **Physical Exam**: Early diastolic murmur at LLSB, Graham Steell (diastolic) murmur 2nd and 3rd left intercostal space increasing with inspiration
- **Investigations**: ECG: RVH; CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV; Echocardiogram: diagnostic
- **Treatment**: Rarely requires treatment; valve replacement (rarely done)
- **Surgical Options**: Pulmonary valve replacement
Figure 39. Hemodynamics of aortic stenosis
Stenosis across the aortic valve results in the generation of a significant pressure gradient between the left ventricle and the aorta and a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure hence diminishing S2.

Figure 40. Hemodynamics of aortic regurgitation
Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2 is audible). The presence of regurgitant blood from the aorta increases left-ventricular end-diastolic volume.

Figure 41. Hemodynamics of acute mitral regurgitation
During systolic contraction, blood regurgitates from the left ventricle into the left atrium across the incompetent mitral valve resulting in an audible holosystolic murmur between S1 and S2. The portion of left ventricular end-diastolic volume that regurgitates into the left atrial myocardium increases left atrial pressures resulting in a tall V-wave (in the JVP).

Figure 42. Hemodynamics of mitral stenosis
First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to mitral stenosis and the consequent generation of a pressure gradient across the left atrium and left ventricle. In diastole the stenotic mitral valve opens which corresponds to the opening snap (OS) and the passage of blood across the mitral stenosis results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible.
Pericardial Disease

Acute Pericarditis

Etiology of Pericarditis/Pericardial Effusion
- idiopathic is most common: presumed to be viral
- infectious
  - viral: Coxsackie virus A, B (most common), echovirus
  - bacterial: *S. pneumoniae, S. aureus*
  - TB
  - fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler's syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin's, breast, lung, renal cell carcinoma, melanoma
- collagen vascular disease: SLE, polyarteritis, rheumatoid arthritis, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (sarcoid)

Signs and Symptoms
- diagnostic triad: chest pain, friction rub, and ECG changes
- pleuritic chest pain: alleviated by sitting up and leaning forward
- pericardial friction rub: may be uni-, bi-, or triphasic
- ± fever, malaise

Investigations
- ECG: initially diffuse elevated ST segments ± depressed PR segment, the elevation in the ST segment is concave upwards → 2-5 d later ST isoelectric with T wave flattening and inversion
- CXR: normal heart size, pulmonary infiltrates
- echo: performed to assess for pericardial effusion

Treatment
- treat the underlying disease
- anti-inflammatory agents (high dose NSAIDs/ASA, colchicine; steroids use controversial), analgesics

Complications
- recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

Pericardial Effusion

Etiology
- transudative (serous)
  - CHF, hypoalbuminemia/hypoproteinemia, hypothyroidism
- exudative (serosanguinous or bloody)
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
- physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

Signs and Symptoms
- may be asymptomatic or similar to acute pericarditis
- dyspnea, cough
- extra-cardiac (esophageal/recurrent laryngeal nerve/tracheo-bronchial/phrenic nerve irritation)
- JVP increased with dominant “x” descent
- arterial pulse normal to decreased volume, decreased pulse pressure
- auscultation: distant heart sounds ± rub
- Ewart's sign

Investigations
- ECG: low voltage, flat T waves, electrical alternans
- CXR: cardiomegaly, rounded cardiac contour
- echo (procedure of choice): fluid in pericardial sac
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, neoplastic involvement

Treatment
- mild: frequent observation with serial echos, treat underlying cause, anti-inflammatory agents
- severe: treat as in tamponade

Acute Pericarditis Triad
- Chest pain
- Friction rub
- ECG changes

Ewart's Sign
Bronchial breathing and dullness to percussion at the lower angle of the left scapula in pericardial effusion due to effusion compressing left lower lobe of lung.
Cardiac Tamponade

Etiology
- major complication of rapidly accumulating pericardial effusion
- cardiac tamponade is a clinical diagnosis
- any cause of pericarditis but especially trauma, malignancy, uremia, proximal aortic dissection with rupture

Pathophysiology
- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

Signs and Symptoms
- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in systolic BP >10 mmHg during quiet breathing)
- JVP "x" descent only, blunted "y" descent
- hepatic congestion/peripheral edema

Investigations
- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- echo: pericardial effusion, compression of cardiac chambers (RA and RV) in diastole
- cardiac catheterization

Treatment
- pericardiocentesis – echo-guided
- pericardiotomy
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO)
- IV fluid may increase CO
- treat underlying cause

Constrictive Pericarditis

Etiology
- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease

Signs and Symptoms
- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
  ▪ ascites, hepatosplenomegaly, edema
- increased JVP, Kussmaul’s sign (paradoxical increase in JVP with inspiration), Friedreich’s sign (prominent "y" descent)
- BP usually normal (and usually no pulsus paradoxus)
- precordial examination: ± pericardial knock (early diastolic sound)
- see Table 17 for differentiation from cardiac tamponade

Investigations
- ECG: non-specific – low voltage, flat T wave, ± AFib
- CXR: pericardial calcification, effusions
- echo/CT/MRI: pericardial thickening
- cardiac catheterization: equalization of end-diastolic chamber pressures (diagnostic)

Treatment
- medical: diuretics, salt restriction
- surgical: pericardiectomy (only if refractory to medical therapy)
- prognosis best with idiopathic or infectious cause and worst in post-radiation; death may result from heart failure

Table 17. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Constrictive Pericarditis</th>
<th>Cardiac Tamponade</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP</td>
<td>&quot;y&quot; &gt; &quot;x&quot;</td>
<td>&quot;x&quot; &gt; &quot;y&quot;</td>
</tr>
<tr>
<td>Kussmaul’s sign</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Pulsus paradoxus</td>
<td>Uncommon</td>
<td>Always</td>
</tr>
<tr>
<td>Pericardial knock</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Variable</td>
<td>Severe</td>
</tr>
</tbody>
</table>
Vascular Disease

- see Vascular Surgery, VS2

Common Medications

Table 18. Commonly Used Cardiac Therapeutics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)</td>
<td>enalapril (Vasotec®),</td>
<td>Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis</td>
<td>HTN, CAD, CHF, post-MI, DM</td>
<td>Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema</td>
<td>Bilateral renal artery stenosis, pregnancy, caution in decreased GFR</td>
</tr>
<tr>
<td></td>
<td>perindopril (Aceon®),</td>
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<tr>
<td></td>
<td>ramipril (Altace®),</td>
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<td></td>
<td>lisinopril (Zestril®)</td>
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<tr>
<td>ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)</td>
<td>candesartan,</td>
<td>Block AT II receptors, causing similar effects to ACEI</td>
<td>Same as ACEI, although evidence is generally less for ARBs; often used when ACEI are not tolerated</td>
<td>Similar to ACEI, but do not cause dry cough</td>
<td>Same as ACEI</td>
</tr>
<tr>
<td></td>
<td>irbesartan,</td>
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<tr>
<td></td>
<td>valsartan</td>
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<tr>
<td>DIRECT RENIN INHIBITORS (DRIs)</td>
<td>aliskiren</td>
<td>Directly blocks renin thus inhibiting the conversion of angiotensinogen to angiotensin I; this also causes a decrease in AT II</td>
<td>HTN (exact role of this drug remains unclear)</td>
<td>Diarrhea, hyperkalemia (higher risk if used with an ACEI), rash, cough, angioedema, reflux, hypotension, rhabdomyolysis, seizure</td>
<td>Pregnancy, severe renal impairment</td>
</tr>
<tr>
<td>β-BLOCKERS</td>
<td>atenolol, metoprolol,</td>
<td>Block β-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand, slow conduction through the AV node</td>
<td>HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AFib, SVT</td>
<td>Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, hyperkalaemia, branchioparalysis, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud’s phenomenon, and Claudication</td>
<td>Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW Caution in asthma, claudication, Raynaud’s phenomenon, and Decompensation CHF</td>
</tr>
<tr>
<td></td>
<td>bisoprolol, labetalol,</td>
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<tr>
<td></td>
<td>carvedilol, acebutalol</td>
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<td></td>
<td>propranolol</td>
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<tr>
<td></td>
<td>labetalol, carvedilol,</td>
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<tr>
<td></td>
<td>acebutalol</td>
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<tr>
<td></td>
<td>metoprolol,</td>
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<tr>
<td></td>
<td>bisoprolol,</td>
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<tr>
<td></td>
<td>labetalol, carvedilol,</td>
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<tr>
<td></td>
<td>acebutalol</td>
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<tr>
<td></td>
<td>propranolol</td>
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<tr>
<td>CALCIUM CHANNEL BLOCKERS (CCBs)</td>
<td>diltiazem</td>
<td>Block smooth muscle and myocardial calcium channels causing effects similar to β-blockers Also vasodilate</td>
<td>HTN, CAD, SVT, diastolic dysfunction</td>
<td>Hypotension, bradycardia, edema Negative inotrope</td>
<td>Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW, CHF</td>
</tr>
<tr>
<td></td>
<td>verapamil</td>
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<tr>
<td></td>
<td>amlodipine (Norvasc®),</td>
<td>Block smooth muscle calcium channels causing peripheral vasodilation</td>
<td>HTN</td>
<td>Hypotension, edema, flushing, headache, light-headedness</td>
<td>Severe aortic stenosis and liver failure</td>
</tr>
<tr>
<td></td>
<td>nifedipine (Adalat®),</td>
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<tr>
<td></td>
<td>felodipine (Plendil®)</td>
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<tr>
<td>DIURETICS</td>
<td>hydrochlorothiazide,</td>
<td>Reduce Na+ reabsorption in the distal convoluted tubule (DCT)</td>
<td>HTN (drugs of choice for uncomplicated HTN)</td>
<td>Hypotension, hypokalemia, polyuria</td>
<td>Sulfate allergy, pregnancy</td>
</tr>
<tr>
<td></td>
<td>chlorothalidone,</td>
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<td></td>
<td>metolazone</td>
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<tr>
<td></td>
<td>furosemide (Lasix®)</td>
<td>Blocks Na+/K+ -ATPase in the loop of Henle</td>
<td>CHF, pulmonary or peripheral edema</td>
<td>Hypovolemia, hypokalemia metabolic alkalosis</td>
<td>Hypovolemia, hypokalemia</td>
</tr>
<tr>
<td></td>
<td>Loop diuretics</td>
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</tr>
<tr>
<td></td>
<td>Aldosterone receptor</td>
<td>Antagonize aldosterone receptors</td>
<td>HTN, CHF, hypokalemia</td>
<td>Edema, hyperkalemia, gynecomastia</td>
<td>Renal insufficiency, hyperkalemia, pregnancy</td>
</tr>
<tr>
<td></td>
<td>antagonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INOTROPES</td>
<td>digoxin (Lanoxin®)</td>
<td>Inhibit Na+/K+ -ATPase, leading to increased intracellular Na+ and Ca2+ concentration and increased myocardial contractility Also slows conduction through the AV node</td>
<td>CHF, AFib</td>
<td>AV block, tachyarrhythmias, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, N/V</td>
<td>2nd or 3rd degree AV block, hypokalemia, WPW</td>
</tr>
</tbody>
</table>
### Table 18. Commonly Used Cardiac Therapeutics (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
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<tr>
<td>Coumarins</td>
<td>warfarin (Coumadin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X</td>
<td>AFib, LV dysfunction, prosthetic valves</td>
<td>Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis</td>
<td>Recent surgery or bleeding, bleeding diathesis, pregnancy</td>
</tr>
<tr>
<td>Heparins</td>
<td>Unfractionated heparin, LMWHs: dalteparin, enoxaparin, tinzaparin</td>
<td>Antithrombin III agonist, leading to decreased clotting factor activity</td>
<td>Acute MI; when immediate anticoagulant effect needed</td>
<td>Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs)</td>
<td>Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>dabigatran, melagatran</td>
<td>Competitive, direct thrombin inhibitor; thrombin enables fibrinogen conversion to fibrin during the coagulation cascade, thereby preventing thrombus development</td>
<td>AFib</td>
<td>Bleeding, GI upset</td>
<td>Severe renal impairment, recent surgery, active bleeding</td>
</tr>
<tr>
<td>Direct Factor Xa inhibitors</td>
<td>rivaroxaban</td>
<td>Direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways</td>
<td>AFib</td>
<td>Bleeding, GI upset, elevated liver enzymes</td>
<td>Hepatic disease, active bleeding, bleeding diathesis, pregnancy, lactation</td>
</tr>
<tr>
<td><strong>ANTIPLATELETS</strong></td>
<td></td>
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</tr>
<tr>
<td>Salicylates</td>
<td>ASA (Aspirin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Irreversibly acetylates platelet COX-1, preventing thromboxane A2-mediated platelet aggregation</td>
<td>CAD, acute MI, post-MI, post-PCI, CABG</td>
<td>Bleeding, GI upset, GI ulceration, impaired renal perfusion</td>
<td>Active bleeding or PUD</td>
</tr>
<tr>
<td>Thienopyridines</td>
<td>clopidogrel (Plavix&lt;sup&gt;®&lt;/sup&gt;), ticlopidine (Ticlid&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Block platelet ADP receptors</td>
<td>Acute MI, post-MI, post-PCI, CABG</td>
<td>Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)</td>
<td>Active bleeding or PUD</td>
</tr>
<tr>
<td>GPIIb/IIIa inhibitors</td>
<td>eptifibatide, tirofiban, abciximab</td>
<td>Block binding of fibrinogen to Gp IIb/IIIa</td>
<td>Acute MI, particularly if PCI is planned</td>
<td>Bleeding</td>
<td>Recent surgery or bleeding, bleeding diathesis</td>
</tr>
<tr>
<td><strong>THROMBOLYTICS</strong></td>
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<tr>
<td>alteplase, reteplase, tenecteplase, streptokinase</td>
<td>Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin</td>
<td>Acute STEMI</td>
<td>Bleeding</td>
<td>See Table 8, C28</td>
<td></td>
</tr>
<tr>
<td><strong>NITRATES</strong></td>
<td>nitroglycerin</td>
<td>Relax vascular smooth muscle, producing venous and arteriolar dilation</td>
<td>CAD, MI, CHF (isosorbide dinitrate plus hydralazine)</td>
<td>Headache, dizziness, weakness, postural hypotension</td>
<td>Concurrent use of cGMP phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure</td>
</tr>
<tr>
<td><strong>LIPID LOWERING AGENTS</strong></td>
<td>statins</td>
<td>Inhibit HMG CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis</td>
<td>Dyslipidemia (1&lt;sup&gt;st&lt;/sup&gt; prevention of CAD), CAD, post-MI</td>
<td>Myalgia, rhabdomyolysis, abdominal pain</td>
<td>Liver or muscle disease</td>
</tr>
</tbody>
</table>
### Antiarrhythmics

![Figure 43. Representative cardiac action potential](image)

#### Table 19. Antiarrhythmic* Drugs (Vaughan-Williams Classification)

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>quinidine, procainamide, disopyramide</td>
<td>SVT, VT</td>
<td>Torsades de Pointes (all Ia), diarrhea</td>
<td>Moderate Na⁺ channel blockade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lupus-like syndrome</td>
<td>Slows phase 0 upstroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anticholinergic effects</td>
<td>Prolongs repolarization, slowing conduction</td>
</tr>
<tr>
<td>Ib</td>
<td>lidocaine, mexiletine</td>
<td>VT</td>
<td>Confusion, stupor, seizures</td>
<td>Mild Na⁺ channel blockade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GI upset, tremor</td>
<td>Shortens phase 3 repolarization</td>
</tr>
<tr>
<td>Ic</td>
<td>propafenone, flecaïnide, encainide</td>
<td>SVT, VT, AFib</td>
<td>Exacerbation of VT (all Ic)</td>
<td>Marked Na⁺ channel blockade</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative intropathy (all Ic)</td>
<td>Markedly slows phase 0 upstroke</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bradycardia and heart block (all Ic)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>propranolol, metoprolol, etc.</td>
<td>SVT, AFib</td>
<td>Bronchospasm, negative intropathy, bradycardia, AV block, impotence, fatigue</td>
<td>β-blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Decreases phase 4 depolarization</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>amiodarone**, sotalol</td>
<td>SVT, VT, AFib</td>
<td>Photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR</td>
<td>Blocks K⁺ channel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Torsades de Pointes, bradycardia, heart block, β-blocker side effects</td>
<td>Prolongs phase 3 repolarization, which prolongs refractory period</td>
</tr>
<tr>
<td>IV</td>
<td>verapamil, diltiazem</td>
<td>SVT, AFib</td>
<td>Bradycardia, AV block, hypotension</td>
<td>Calcium channel blocker</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Deceases phase 4 spontaneous depolarization, slowing AV node conduction</td>
<td></td>
</tr>
</tbody>
</table>

*All antiarrhythmics have potential to be proarrhythmic  **Amiodarone has class I, II, III, and IV properties

#### Table 20. Actions of α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>Target System</th>
<th>α1</th>
<th>α2</th>
<th>β1</th>
<th>β2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Constriction of vascular smooth muscle</td>
<td>Same as α₁</td>
<td>Increased myocardial contractility, Accelerate SA node</td>
<td>Decreased vascular smooth muscle tone</td>
</tr>
<tr>
<td></td>
<td>Constriction of skin, skeletal muscle, and sphincteric vessels</td>
<td></td>
<td>Accelerate ectopic pacemakers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased myocardial contractility</td>
<td>Peripherally act to modulate vessel tone</td>
<td>Vasoconstrict and dilate, oppose α₁ vasoconstrictor activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased heart rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pilomotor smooth muscle contraction</td>
<td></td>
<td></td>
<td>Bronchodilation</td>
</tr>
<tr>
<td>Dermal</td>
<td>Apocrine constriction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>Radial muscle contraction</td>
<td></td>
<td></td>
<td>Ciliary muscle relaxation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Inhibition of myenteric plexus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
<td></td>
<td>Stimulation of renal renin release</td>
<td>Bladder wall relaxation</td>
</tr>
<tr>
<td></td>
<td>Anal sphincteric contraction</td>
<td></td>
<td></td>
<td>Uterine relaxation</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Pregnant uterine contraction</td>
<td></td>
<td>Same as α₁</td>
<td>Fat cell lipolysis</td>
</tr>
<tr>
<td></td>
<td>Female and seminal vesicle ejaculation</td>
<td></td>
<td>Fat cell lipolysis</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td></td>
<td>Urinary bladder contraction</td>
<td></td>
<td>Glycogenolysis</td>
<td>Fat cell lipolysis</td>
</tr>
<tr>
<td></td>
<td>Stimulate liver glycogenolysis and glycoconjugation at the liver</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)
Table 21. Commonly Used Drugs that Act on α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>α RECEPTORS</th>
<th>β RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α1</td>
<td>α1 and α2</td>
</tr>
<tr>
<td>Agonist</td>
<td>Phenylephrine</td>
<td>Epinephrine</td>
</tr>
<tr>
<td></td>
<td>Methoxamine</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prazosin</td>
<td>Phentolamine</td>
</tr>
<tr>
<td></td>
<td>Phenoxymethylamine</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the Family Practice Notebook (http://www.fpnotebook.com/NEU194.htm)

Landmark Cardiac Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISCHEMIC HEART DISEASE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Lancet 2003; 361:1149-58</td>
<td>In hypertensive patients with risk factors for CHD and average or below-average cholesterol, atorvastatin reduced nonfatal MI, fatal CHD, fatal/nonfatal stroke, coronary events but not all-cause mortality</td>
</tr>
<tr>
<td>CAPRIE</td>
<td>Lancet 1996; 348:1329-39</td>
<td>In atherosclerotic vascular disease clopidogrel reduced the primary combined endpoint of stroke, MI, or vascular death and improved PAD compared to ASA</td>
</tr>
<tr>
<td>CARE</td>
<td>NEJM 1996; 335:1001-9</td>
<td>Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol</td>
</tr>
<tr>
<td>COURAGE</td>
<td>NEJM 2007; 356:1503-16</td>
<td>Compared with optimal medical therapy alone PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events</td>
</tr>
<tr>
<td>CURE</td>
<td>NEJM 2001; 345:494-502</td>
<td>Clopidogrel plus ASA reduced death from CV causes, non fatal MI, or stroke but increased bleeding complications</td>
</tr>
<tr>
<td>EUROPA</td>
<td>Lancet 2003; 362:782-88</td>
<td>With stable CAD and no CHF perindopril reduced cardiovascular death, MI, and total mortality</td>
</tr>
<tr>
<td>HOPE</td>
<td>NEJM 2000; 342:154-60</td>
<td>In high-risk patients without low LVEF or CHF ramipril reduced rates of death, MI, stroke, revascularization, new diagnosis of DM and complications due to DM; vitamin E had no effect on outcomes</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002; 360:7-22</td>
<td>In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths, and major vascular events</td>
</tr>
<tr>
<td>JUPITER</td>
<td>NEJM 2008; 359:2195-2207</td>
<td>With low to normal LDL-C and elevated hsCRP treatment with rosuvastatin significantly reduced major cardiovascular events; NNT with rosuvastatin for 2 yr to prevent one primary endpoint = 95</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>NEJM 2009; 360:961-972</td>
<td>CABG has lower rate of major cardiac or cerebrovascular events; the rate of stroke was increased with CABG, whereas the rate of repeat revascularization was increased with PCI</td>
</tr>
<tr>
<td>TNT</td>
<td>NEJM 2005; 352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d</td>
</tr>
<tr>
<td>WHI</td>
<td>JAMA 2002; 288:321-333</td>
<td>Estrogen plus progestin therapy is associated with increased risks of cardiovascular disease and breast cancer but decreased risks of hip fracture and colorectal cancer in postmenopausal women</td>
</tr>
</tbody>
</table>

MYOCARDIAL INFARCTION

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHAT</td>
<td>JAMA 1982; 247:1707-14</td>
<td>In acute MI propranolol reduced all-cause mortality, cardiovascular death, and sudden death from atherosclerotic heart disease</td>
</tr>
<tr>
<td>COURAGE</td>
<td>NEJM 2007; 356:1503-16</td>
<td>Compared with optimal medical therapy alone PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events</td>
</tr>
<tr>
<td>ISIS-2</td>
<td>Lancet 1988; 2:349-60</td>
<td>Early therapy with streptokinase and ASA in patients with MI individually and in combination significantly reduced all-cause mortality and in combination demonstrated additive effect</td>
</tr>
<tr>
<td>ISIS-4</td>
<td>Lancet 1995; 345:669-85</td>
<td>In patients with suspected or definite acute MI early treatment with captopril reduced all-cause mortality at 35 d and during long-term follow up</td>
</tr>
<tr>
<td>OASIS-5</td>
<td>NEJM 2006; 354:1464-76</td>
<td>Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 and MI at 30 and 180 d</td>
</tr>
<tr>
<td>PROVE IT – TIMI 22</td>
<td>NEJM 2004; 350:1495-1504</td>
<td>In patients hospitalized for ACS high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin</td>
</tr>
<tr>
<td>Trial</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>AIRE</td>
<td><em>Lancet</em> 1993; 342:821-8</td>
<td>Ramipril commenced 3-10 d after MI and continued for a mean 15-month period significantly reduced all-cause mortality in patients with non-severe CHF</td>
</tr>
<tr>
<td>CIBIS II</td>
<td><em>Lancet</em> 1999; 353:9-13</td>
<td>Bisoprolol reduced all-cause mortality, cardiovascular death, all-cause hospitalization, and CHF hospitalization</td>
</tr>
<tr>
<td>COMET</td>
<td><em>Lancet</em> 2003; 362:7-13</td>
<td>Carvedilol was associated with a reduction in all cause mortality compared with metoprolol</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td><em>NEJM</em> 1987; 316:1429-35</td>
<td>Enalapril reduced all-cause mortality, death due to progression of heart failure</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td><em>NEJM</em> 2001; 344:1651-8</td>
<td>Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td><em>NEJM</em> 2008; 359:2456-2467</td>
<td>In patients with CHF and normal LVEF treatment with ARB (irbesartan) did not improve mortality or cardiovascular morbidity compared to placebo</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td><em>Lancet</em> 1999; 353:2001-7</td>
<td>Metoprolol CR/XL daily in addition to optimum standard therapy improved survival in clinically stable patients equating to prevention of 1 death per 27 patients treated per year</td>
</tr>
<tr>
<td>RALES</td>
<td><em>NEJM</em> 1999; 341:709-17</td>
<td>In severe CHF (class II/IV) and LVEF &lt;35%, spironolactone reduced all-cause mortality, sudden death, and death due to progression of heart failure</td>
</tr>
<tr>
<td>SAVE</td>
<td><em>NEJM</em> 1992; 327:669-77</td>
<td>Patients with LV dysfunction post-MI long-term captopril over 3.5 yr reduced the risk of death due to cardiovascular causes, recurrent MI, development of severe CHF, and CHF hospitalization</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td><em>NEJM</em> 2005; 352:225-237</td>
<td>In mild-to-moderate CHF shock-only ICD significantly reduces risk of death; amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF</td>
</tr>
<tr>
<td>SOLVD</td>
<td><em>NEJM</em> 1991; 325:293-302</td>
<td>In stable chronic CHF with decreased LVEF (&lt;0.35) long-term enalapril reduced death due to all causes and death or hospitalization due to CHF</td>
</tr>
<tr>
<td>TRACE</td>
<td><em>NEJM</em> 1995; 333:1670-6</td>
<td>In patients with LV dysfunction post-MI long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td><em>NEJM</em> 1991; 325:303-10</td>
<td>In chronic CHF enalapril reduced mortality more than hydralazine-isosorbide for at least 2 yr; treatment with either enalapril or hydralazine-isosorbide increased LVEF</td>
</tr>
</tbody>
</table>

**DIABETES**

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDS</td>
<td><em>Lancet</em> 2004; 264:685-96</td>
<td>Atorvastatin reduces the risk of cardiovascular events in patients with type 2 DM</td>
</tr>
<tr>
<td>ONTARGET</td>
<td><em>NEJM</em> 2008; 358:1547-59</td>
<td>In patients with vascular disease or DM without CHF telmisartan is equally as effective as ramipril, with telmisartan causing a reduced risk of cough and angioedema, and an increased risk of hypotensive symptoms; combination therapy offers no advantage</td>
</tr>
</tbody>
</table>

**ARRHYTHMIA**

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFFIRM</td>
<td><em>NEJM</em> 2002; 347:1825-33</td>
<td>No significant difference in mortality rates between rate or rhythm control of AFib</td>
</tr>
<tr>
<td>AF-CHF</td>
<td><em>NEJM</em> 2008; 358:2867-77</td>
<td>In patients with AFib and CHF there is no significant difference in mortality rates from cardiovascular causes between rate and rhythm control</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td><em>NEJM</em> 2011; 365:883-891</td>
<td>In patients with AFib rivoxabarin is non-inferior to warfarin for stroke prevention, and major and non-major bleeding</td>
</tr>
</tbody>
</table>

**HYPERTENSION**

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYVET</td>
<td><em>NEJM</em> 2008; 358:1887-98</td>
<td>In hypertensive patients &gt;80 yr treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non-fatal stroke</td>
</tr>
<tr>
<td>UKHD (UKPOS)</td>
<td><em>BMJ</em> 1998; 317:703-13</td>
<td>Hypertensive patients with DM and tight BP control at &lt;150/85 mmHg by use of ACEI or β-blocker reduced risk of diabetic complications and death related to DM and reduced risk of end-organ damage</td>
</tr>
<tr>
<td>VALUE</td>
<td><em>Lancet</em> 2004; 363:2022-2031</td>
<td>Valsartan group had higher incidence of MI than amlodipine group, whereas amlodipine had a higher incidence of new-onset DM</td>
</tr>
</tbody>
</table>
Clinical Pharmacology

Tara He and Vivian Wang, chapter editors
Jillian Bardsley and Evan Lilly, associate editors
Ilya Mukovozov, EBM editor
Dr. David Juurlink, staff editor

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Common Drug Endings

References

Acronyms
ACE angiotensin converting enzyme
ACCh acetylcholine
ADR adverse drug reaction
ARB angiotensin receptor blocker
BBB blood brain barrier
Cl clearance
Cr creatinine
CSF cerebrospinal fluid
CSFa certain safety factor
CYP cytochrome P450 protein
DN drug identification number
F bioavailability
GFR glomerular filtration rate
NDC national drug code
NE norepinephrine
Pp partition coefficient of a drug
PD pharmacodynamics
PDE phosphodiesterase
Pgp p-glycoprotein
PK pharmacokinetics
TBW total body water
TDM therapeutic drug monitoring
TI therapeutic index
Vd volume of distribution
General Principles

Drug Nomenclature

- **chemical name**: describes chemical structure; same in all countries (e.g. \(N\)-(4-hydroxyphenyl)acetamide is acetaminophen)
- **DIN or NDC**: DIN assigned by Health Canada; NDC assigned by FDA (US)
- **non-proprietary name**: approved name (post-phase III trial), official name (listed in pharmacopoeia), or generic name (off-patent) (e.g. acetaminophen)
- **proprietary (trade) name**: the brand name or registered trademark (e.g. Tylenol®)

Phases of Clinical Testing

- **phase I**: first administration to healthy human volunteers, following animal studies; to determine PK and PD
- **phase II**: first administration to patients, small sample sizes; to determine initial safety and effectiveness, dose range, PK, PD
- **phase III**: large sample sizes, often double-blind RCT; comparative (new drug vs. placebo or standard of care) to establish safety and efficacy
- **phase IV**: post-marketing surveillance, wide distribution; to determine rare ADRs, effects of long-term use, ideal dosing, effects in real world practice

Drug Administration

- choice of route of administration depends on: drug properties, local and systemic effects (limiting action or adverse events), desired onset and/or duration of action, patient characteristics

Table 1. Routes of Drug Administration

<table>
<thead>
<tr>
<th>Route</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (PO)</td>
<td>Convenient, easy to administer</td>
<td>Drug metabolism by GI secretions</td>
</tr>
<tr>
<td></td>
<td>Large surface area for absorption</td>
<td>Incomplete absorption</td>
</tr>
<tr>
<td></td>
<td>Inexpensive relative to parenteral administration</td>
<td>Hepatic first-pass effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potential GI irritation</td>
</tr>
<tr>
<td>Buccal/Sublingual (SL)</td>
<td>Rapid onset of action</td>
<td>Must be lipid-soluble, non-irritating</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Short duration of action</td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>Almost no hepatic first-pass effect</td>
<td>Inconvenient, irritation at site of application</td>
</tr>
<tr>
<td></td>
<td>Use when NPO, vomiting, or unconscious</td>
<td>Erratic absorption</td>
</tr>
<tr>
<td>Intravenous (IV)</td>
<td>No hepatic first-pass effect</td>
<td>Hard to remove once administered</td>
</tr>
<tr>
<td></td>
<td>Slow infusion or rapid onset of action</td>
<td>Risk of infection, bleeding, vascular injury, extravasation</td>
</tr>
<tr>
<td></td>
<td>Easy to titrate dose</td>
<td>Expensive</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>Depot storage if oil-based = slow release of drug Aqueous solution = rapid onset of action</td>
<td>Pain at site of injection</td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>Non-irritating drugs, small volumes</td>
<td>Pain at site of injection</td>
</tr>
<tr>
<td></td>
<td>Constant, even absorption</td>
<td>Smaller volumes than IM</td>
</tr>
<tr>
<td></td>
<td>Alternative to IV</td>
<td>May have tissue damage from multiple injections</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Direct into CSF Bypass BBB and blood-CSF barrier</td>
<td>Risk of infection</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Immediate (local) action in lungs</td>
<td>Must be a gas, vapour, or aerosol</td>
</tr>
<tr>
<td></td>
<td>Rapid delivery to blood (systemic action)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>Easy to administer Localized (limited systemic absorption)</td>
<td>Effects are mainly limited to site of application</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Drug absorption through intact skin</td>
<td>Irritation at site of application</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Delayed onset of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrophilic drugs are not easily absorbed</td>
</tr>
<tr>
<td>Others (intraperitoneal, intra-articular)</td>
<td>Local effect</td>
<td>Risk of infection</td>
</tr>
</tbody>
</table>
Pharmacokinetics

- study of “what the body does to a drug”
- definition: relationship between drug administration, time-course/rate of absorption and distribution, concentration changes in the body compartments, and the drug’s removal from the body

Absorption

- definition: movement of the drug from the site of administration into plasma

Mechanisms of Drug Absorption

- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms: active transport, facilitated diffusion, pinocytosis/phagocytosis

Factors Affecting the Rate and Extent of Drug Absorption

- Po/w (i.e. its relative solubility in oil/lipid vs. water)
- local blood flow at the site of administration (e.g. sublingual vessels facilitate rapid absorption of SL medications)
- molecular size (e.g. small molecular weight drugs absorb faster)
- pH and drug ionization
  - drugs are usually weak acids (e.g. ASA) or weak bases (e.g. ketoconazole) and thus have both ionized and non-ionized forms
  - body compartment pH and drug pKa determine the ratio of ionized:non-ionized ratio (using the Henderson-Hasselbach equation)
  - non-ionized forms cross cell membranes much faster than ionized (charged) forms
- total surface area for absorption
  - small intestinal villi (large surface area) is the primary site of absorption for most oral drugs

Bioavailability

- definition: fraction of dose after administration that reaches systemic circulation in an unchanged state
- decreased by: drug absorption, gut metabolism, and hepatic first-pass effect
- IV dose has 100% bioavailability (F = 1)

First-Pass Effect

- definition: drug metabolism by the liver and sometimes the gut before it reaches systemic circulation, resulting in reduced F
- occurs with PO administration of a drug: GI tract (absorption) → portal vein to liver (first-pass metabolism) → systemic circulation
- occurs to much lesser extent with PR administration because drug absorbed in colon bypasses the portal system: colon (absorption) → internal pudendal veins → IVC → systemic circulation

Efflux Pump

- Pgp is a protein in the GI tract, renal epithelium, and elsewhere that acts as a multidrug efflux pump involved in the transport of drugs out of cells
- acts to oppose intestinal absorption and enhance renal elimination of certain drugs (e.g. digoxin, dabigatran, etexilate, etoposide, paclitaxel, tacrolimus, cyclosporine)
- some drugs (e.g. macrolide antibiotics) inhibit Pgp function, leading to increased levels of Pgp substrates; Pgp inducers (e.g. St. John’s wort) do the opposite
- some tumors overexpress Pgp leading to multidrug resistance to chemotherapy agents

Distribution

- definition: movement of drugs between different body compartments and to the site of action
- major body fluid compartments: plasma, interstitial fluid, intracellular fluid, transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments: fat, brain
Factors Affecting the Rate and Extent of Drug Distribution
- physiochemical properties of the drug (e.g. $P_{ow}$)
- pH of fluid
- plasma protein binding
- binding within compartments (i.e. depots)
- regional blood flow

Volume of Distribution
- maximum actual $V_d$ (anatomic fluid volume accessible to drug) = TBW (TBW~40 L for average adult)
- $V_d$: the apparent volume of fluid into which a drug dissolves
  - a calculated value = amount of drug in body ÷ plasma drug concentration
  - a theoretical value that does not correspond to an anatomical space (i.e. can exceed TBW)
  - small $V_d$ corresponds to a drug which concentrates in plasma and/or binds plasma proteins to a high degree
  - large $V_d$ corresponds to a drug that distributes into tissues (fat, muscle, etc.); most is not in blood (measured) space, and it therefore “appears” to distribute in a large volume
- $V_d$ of plasma-protein bound drugs can be altered by liver and kidney disease
- example: amiodarone distributes into TBW (actual $V_d = 40$ L), but it also concentrates in fat tissues giving instead an apparent $V_d$ of 400 L; therefore, to achieve a given plasma concentration of amiodarone, we dose as though the drug distributes into 400 L of body fluid

Plasma Protein Binding
- drug molecules in the blood exist in an equilibrium of two forms:
  1. bound to plasma protein: acidic drugs bind to albumin, basic drugs bind to α1-acid glycoprotein
  2. free or unbound: can leave the circulation to distribute into tissues and exert an effect, subject to metabolism and elimination
- bound fraction is determined by drug concentration, binding affinity, and plasma protein concentration (number of binding sites)
- reduced number of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in an increased concentration of free drug, which is often metabolized with no harmful effects, although toxicity is possible

Depots
- a body compartment where drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wk)

Barriers (Relative)
- body structures that limit or prevent diffusion of drug molecules, such as the placenta or BBB (a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. Pgp), which serve as a natural defense mechanism against drugs and xenobiotics
- need to consider dosing route if drugs are meant to cross these barriers

Metabolism (Biotransformation)
- definition: chemical transformation of a drug in vivo to make it more hydrophilic to enhance renal elimination
- sites of biotransformation: liver (main), GI tract, lung, plasma, kidney
- as a result of the process of biotransformation
  - a pro-drug may be activated (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be changed to another active metabolite (e.g. diazepam to oxazepam)
  - a drug may be changed to a toxic metabolite (e.g. meperidine to normeperidine)
  - a drug may be inactivated (most drugs)
Drug Metabolizing Pathways
- **phase I (P450) reactions**
  - small molecular changes introduce or unmask polar chemical groups on a parent compound to increase its water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation); the change in \( P_{w/w} \) is typically minimal compared to phase II, and often phase I places a polar "handle" on a lipophilic drug to allow for phase II
  - mediated by CYPs found in the endoplasmic reticulum
  - product of the reaction can be excreted or undergo further phase II reactions

- **phase II (conjugation) reactions**
  - conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
  - dramatically increases water solubility and renal elimination
  - sometimes results in biologically active metabolites (e.g. glucuronides of morphine)
  - can occur independently of phase I reactions

Factors Affecting Drug Biotransformation
- **genetic polymorphism** of metabolizing enzymes
  - individual genotypes may determine rate of drug metabolism (e.g. poor, intermediate, extensive, or ultrarapid metabolizers)
  - may lead to toxicity or ineffectiveness of a drug at a normal dose
    - tamoxifen and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas overactive/duplicated alleles impart "ultrarapid metabolizer" phenotype)
    - warfarin is metabolized by CYP2C9 (nonfunctional alleles lead to greater effect and lower dose requirements)
- **enzyme inhibition** may sometimes be due to other drugs
  - CYP inhibition leads to an increased concentration and bioavailability of the substrate drug (e.g. erythromycin [CYP3A4 inhibitor], can predispose patients to simvastatin toxicity [metabolized by CYP3A4])
- **enzyme induction**
  - certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
    - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCP and bilirubin) by inducing the CYP system
  - **liver dysfunction** (e.g. hepatitis, alcoholic liver, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but this may not be clinically significant due to the liver’s reserve capacity
  - **renal disease** often results in decreased drug clearance
  - **extremes of age** (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
  - **nutrition**: insufficient protein and fatty acid intake decreases CYP biotransformation, and vitamin/mineral deficiencies may also impact metabolizing enzymes
  - **alcohol**: while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1 and increase the risk of hepato cellular damage from acetaminophen by increasing the generation of acetaminophen’s toxic metabolite
  - **smoking**: can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. theophylline)

Elimination
- definition: removal of drug from the body

Routes of Drug Elimination
- **kidney** (main organ of elimination): two mechanisms
  1. **glomerular filtration**
    - a passive process, so that only the free drug fraction can be filtered
    - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
  2. **tubular secretion**
    - an active process that is saturable, allowing both protein-bound and free drug fractions to be excreted
    - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
    - drugs may competitively block mutual secretion if both use the same secretion system (e.g. probenecid can be used to reduce the excretion of penicillin)
- **tubular reabsorption**: drugs can be passively reabsorbed back to the systemic circulation, counteracting elimination mechanisms
- **renal function** (decreases with age and is affected by many disease states) is assessed clinically using serum Cr levels
- **stool**: some drugs and metabolites are actively excreted in the bile (e.g. corticosteroids) or directly into the intestinal tract
  - enterohepatic reabsorption counteracts stool elimination, and thus can substantially prolong the drug’s duration in the body
  - some glucuronic acid conjugates that are excreted in the bile will be hydrolyzed in the intestines by bacteria back to its original form that can be systemically reabsorbed
- **lungs**: elimination of anesthetic gases and vapours by exhalation
- **saliva**: saliva concentrations of some drugs parallel their plasma levels (e.g. rifampin)

### Pharmacokinetic Calculation

- **definition**: the quantitative description of the rates of the various steps of drug disposition (i.e. how drugs move through the body)
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism, and elimination) can be graphically represented on a concentration vs. time graph

### Time-Course of Drug Action

- many kinetic parameters are measured using IV dosing, such that absorption is immediate and distribution for most drugs is rapid; thus elimination is the main process being measured
- the concentration axis is converted to a log10 concentration to allow for easier mathematical calculations

#### Half-Life

- **definition**: time taken for the serum drug level to fall 50% during elimination
- drugs with first order kinetics require five half-lives to reach steady state with repeated dosing or for complete drug elimination once dosing is stopped

<table>
<thead>
<tr>
<th># of Half-Lives</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>3.3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Steady State Concentration</td>
<td>50%</td>
<td>75%</td>
<td>87.5%</td>
<td>90%</td>
<td>93.8%</td>
<td>96.9%</td>
</tr>
</tbody>
</table>

### Steady State

- drug concentration stays constant when the same amount of drug entering the system is eliminated from the system
- appropriate timing is important for therapeutic monitoring since drug levels are reliable only when the drug has reached steady state
- **special situations**
  - use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
  - use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect and multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, insulin, unfractionated heparin)

### Clearance

- a quantitative measurement of the body fluid volume from which a substance is removed per unit time
- Cl = rate of elimination of drug / plasma drug concentration
- must consider Cl from a specific part of the body and total body Cl

### Elimination Kinetics

- **first-order kinetics** (most common type)
  - constant fraction of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the Cl decreases
  - becomes linear relationship when plotted on a log(concentration) vs. time graph
- **zero-order kinetics** (less common, associated with toxicities, e.g. alcohol)
  - a constant rate of drug eliminated regardless of concentration; concept of half-life does not apply
  - the concentration axis is converted to a log (concentration) to allow for easier mathematical calculations

### The Cockcroft-Gault Equation

Estimate CrCl in Adults 20 yr of age and older

- For males
  \[ \text{CrCl (mL/min)} = \left( \frac{140 - \text{age in yr}}{\text{Weight (kg)}} \times 1.2 \right) \times \text{serum Cr (µmol/L)} \]
- For females, multiply above equation by 0.85
- Only applies when renal function is at steady state

### Principles of Pharmacokinetics

- **Vd** = amount of drug in the body / plasma drug concentration
- **Cl** = rate of elimination of drug / plasma drug concentration
- **Half-life** (t½) = 0.7xVd/Cl

For most drugs it takes 5 half-lives to reach steady state with repeated dosing or to eliminate a drug once dosing is stopped
### Pharmacodynamics

#### Dose-Response Relationship

**Efficacy**
- the ability of a drug to produce a response after binding to its cognate receptor
- measured by \( E_{\text{max}} \) (the maximal response that a drug can elicit in a RCT or under optimal circumstances)

**Potency**
- measured by \( EC_{50} \) (the concentration of a drug needed to produce 50% of \( E_{\text{max}} \))
- a drug that reaches its \( EC_{50} \) at the lower dose is more potent

![Figure 6. log(dose)-response curve illustrating efficacy and potency](image)

**Effects of Drugs on Receptors**

**Agonists**
- drugs that have both affinity and efficacy for their cognate receptors
  - **affinity**: the ability of the agonist to bind to the receptor (e.g. the \( \beta_2 \)-agonist salbutamol has greater affinity for \( \beta_2 \)-receptors than \( \beta_1 \)-receptors)
  - **efficacy**: the ability to recapitulate endogenous response via the receptor interaction (e.g. binding of salbutamol to \( \beta_2 \)-receptors results in smooth muscle relaxation)
- **full agonists**: can elicit a maximal effect at a receptor
- **partial agonists**: can only elicit a partial effect, no matter how high the concentration (i.e. reduced efficacy compared to full agonists) at the receptor

**Antagonists**
- drugs that block the action of an agonist or of an endogenous ligand
  - **chemical antagonism**: direct chemical interaction between agonist and antagonist prevents agonist-receptor binding (e.g. chelating agents for removal of heavy metals)
  - **functional antagonism**: two agonists that act independently at different receptors and have opposite physiological effects (e.g. acetylcholine at the muscarinic receptor compared to epinephrine at the adrenergic receptor)
- **reversible competitive and irreversible antagonism**
  - drugs that have affinity but no efficacy for their cognate receptors, and therefore, exert no effect upon binding
  - reversible competitive antagonists reversibly bind to the same receptor as the agonist, thus displacing it (e.g. naloxone is an antagonist to morphine or heroin)
irreversible antagonists irreversibly bind to the same receptor as the agonist, blocking it from binding (e.g. phenoxybenzamine forms a permanent covalent bond with adrenergic receptors preventing adrenaline and NE from binding)

- **non-competitive antagonism**
  - antagonists bind to an alternate site separate but near the agonist site, producing allosteric effects that change the ability of the agonist to bind (e.g. organophosphates irreversibly bind acetylcholinesterase)

Effectiveness and Safety

**Effectiveness**
- $ED_{50}$ (Effective Dose): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

**Safety**
- $LD_{50}$ (Lethal Dose): the dose of a drug needed to cause death in 50% of a test population of subjects
- $TD_{50}$ (Toxic Dose): the dose needed to cause a harmful effect in 50% of a test population of subjects
**Therapeutic Indices**

**Therapeutic Index: \( \text{TD}_{50}/\text{ED}_{50} \)**
- reflects the “margin of safety” for a drug – the likelihood of a therapeutic dose to cause serious toxicity or death
- the larger the TI, the safer a drug (e.g. warfarin has a narrow TI and requires accurate therapeutic monitoring)
- factors that can change the TI
  - presence of interacting drugs
  - changes in drug absorption, distribution, metabolism, elimination

**Certain Safety Factor: \( \text{TD}_{1}/\text{ED}_{99} \)**
- CSFa >1 translates to a dose effective in at least 99% of the population and toxic in less than 1% of the population

---

**Therapeutic Drug Monitoring**

- definition: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance)
  - serum drug samples are usually taken when the drug has reached steady state (after approximately 5 half-lives)
  - TDM is often used for drugs that have: narrow TIs, unpredictable dose-response relationships, significant consequences associated with therapeutic failure or toxicity, wide inter-patient pharmacokinetic variability

**Adverse Drug Reactions**

**Table 3. Characteristics of Type A-E Adverse Drug Reactions**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Augmented)</td>
<td>Dose related</td>
<td>Predictable extension of drug’s pharmacologic effect (e.g. β-blockers causing bradycardia)</td>
</tr>
<tr>
<td>B (Bizarre)</td>
<td>Non-dose related</td>
<td>Reactions unrelated to the known pharmacological actions of the drug</td>
</tr>
<tr>
<td>C (Chronic)</td>
<td>Dose and time related</td>
<td>Related to cumulative doses, Effects are well-known and can be anticipated (e.g. femur fracture from bisphosphonates)</td>
</tr>
<tr>
<td>D (Delayed)</td>
<td>Time related</td>
<td>Occurs some time after use of drug (e.g. carcinogen)</td>
</tr>
<tr>
<td>E (End of Use)</td>
<td>Withdrawal</td>
<td>Occurs after cessation of drug use (e.g. opiate withdrawal)</td>
</tr>
</tbody>
</table>

---

In the US, 700,000 emergency department visits and 120,000 hospitalizations are due to ADRs annually.
Approach to Suspected Adverse Drug Reactions

- history and physical exam: signs and symptoms of the reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, dechallenge (response when drug is removed) and rechallenge (response when drug is given again)
- differentiate between drug therapy vs. disease pathophysiology
- treatment: stop the drug, supportive care, symptomatic relief
- resources: check recent literature, FDA; contact the pharmaceutical company; call Poison Control (1-800-222-1222) if overdose or poisoning suspected; check with Motherisk (www.motherisk.org) in cases involving pregnant or breastfeeding women
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity
  - FDA Adverse Event Reporting System available for reporting

Variability in Drug Response

- recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
- possible causes of individual variability in drug response include problems with:
  - intake: patient adherence
  - pharmacokinetics
    - absorption: vomiting, diarrhea or steatorrhea; first pass effect increased due to enzyme induction or decreased due to liver disease
    - drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, and fluoroquinolones)
  - distribution: very high or low percentage body fat; intact or disrupted BBB; patient is elderly or a neonate, or has liver dysfunction
  - biotransformation and elimination: certain genetic polymorphisms or enzyme deficiencies related to drug metabolism (e.g. acetylcholinesterase deficiency, CYP polymorphism); kidney or liver dysfunction
  - pharmacodynamics: genetic variability in drug response (e.g. immune-mediated reactions); diseases that affect drug pharmacodynamics; drug tolerance or cross-tolerance

Drug Interactions

- concomitant prescriptions: one drug alters the effect of another by changing its PK and/or PD
- PK interactions involve
  - absorption: alterations in gastrointestinal pH, gastric emptying, intestinal motility, gut mucosal function
  - biotransformation: alterations in drug metabolizing enzymes
  - excretion: alterations in renal elimination
- PD interactions are due to two drugs that exert similar effects (additive) or opposing effects (subtractive)
- drug interactions can also involve herbal medications (e.g. St. John’s wort) and food (e.g. grapefruit)

Autonomic Pharmacology

- Peripheral Nervous System
  - Somatic
  - Autonomic (ANS)
    - Sympathetic (SNS)
      - Fight or Flight
    - Parasympathetic (PNS)
      - Rest and Digest

Sample of Clinically Relevant Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug(s)</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>β-blockers</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>A</td>
<td>ACEIs</td>
<td>Cough</td>
</tr>
<tr>
<td>A</td>
<td>NSAIDs</td>
<td>GI bleeding</td>
</tr>
<tr>
<td>A</td>
<td>Opiates</td>
<td>GI upset, constipation, urinary retention, respiratory depression</td>
</tr>
<tr>
<td>B</td>
<td>Acetaminophen</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>B</td>
<td>Vancomycin</td>
<td>Red Man syndrome</td>
</tr>
<tr>
<td>A</td>
<td>Aminoglycosides</td>
<td>Ototoxicity and nephrotoxicity</td>
</tr>
<tr>
<td>B</td>
<td>Sulfasalazine</td>
<td>Stevens-Johnson syndrome, Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>B</td>
<td>Penicillins</td>
<td>Rash</td>
</tr>
<tr>
<td>B</td>
<td>Valproic acid, Chinese herbs</td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>

Sulfa-Containing Medications
- Sulfamethoxazole
- Sulfasalazine
- Dapsone

Examples of Clinically Relevant Drug Interactions

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Potential Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin plus ciprofloxacin, clarithromycin, erythromycin, metronidazole or trimethoprim-sulfamethoxazole</td>
<td>Increased effect of warfarin</td>
</tr>
<tr>
<td>Oral contraceptive pills plus rifampin, antibiotics</td>
<td>Decreased effectiveness of oral contraception</td>
</tr>
<tr>
<td>Sildenafil plus nitrates</td>
<td>Hypotension</td>
</tr>
<tr>
<td>SSRI plus St. John’s wort, naratriptan, riociguat, sumatriptan, zolmitriptan</td>
<td>Serotonin syndrome</td>
</tr>
<tr>
<td>Some HMG-CoA reductase inhibitors plus niacin, gemfibrozil, erythromycin or itraconazole</td>
<td>Possible rhabdomyolysis</td>
</tr>
</tbody>
</table>
the autonomic nervous system is divided into sympathetic and parasympathetic divisions
most organs are innervated by both sympathetic and parasympathetic nerves which have
opposing effects (see Neurology, N6)
• ACh and NE are the main neurotransmitters of the autonomic NS
• ACh binds to cholinergic receptors, which include nicotinic and muscarinic receptors
• NE binds to adrenergic receptors, which include β1, β2, α1, and α2
• ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the
plasma by pseudocholinesterase
  • acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) are used to increase
ACh levels in conditions such as myasthenia gravis and Alzheimer’s disease
• NE action is terminated by reuptake by the presynaptic membrane, diffusion from the synaptic
cleft, and degradation by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT)

### Parasympathetic Nervous System

• blood vessels, sweat glands, spleen capsule, and adrenal medulla do NOT have parasympathetic
innervation
• parasympathetic pre-ganglionic fibers originate in the lower brainstem from cranial nerves III,
VII, IX, X, and in the sacral spinal cord at levels S2-S4 and connect with post-ganglionic fibers
via nicotinic receptors in ganglionic cells located near or within the target organ
• post-ganglionic fibers connect with effector tissues via:
  • M₁ muscarinic receptors located in the CNS
  • M₂ muscarinic receptors located in smooth muscle, cardiac muscle, and glandular
epithelium

### Sympathetic Nervous System

• sympathetic pre-ganglionic fibers originate in the spinal cord at spinal levels T1-L3
• pre-ganglionic fibers connect with post-ganglionic fibers via nicotinic receptors located in one
of two groups of ganglia
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral
column
  2. pre-vertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
• post ganglionic fibers connect with effector tissues via
  • β₁ receptors in cardiac tissue
  • β₂ receptors in smooth muscle of bronchi and GI tract
  • α₁ receptors in vascular smooth muscle
  • α₂ receptors in vascular smooth muscle
  • M₃ muscarinic receptors located in sweat glands

<table>
<thead>
<tr>
<th>Table 4. Direct Effects of Autonomic Innervation on the Cardiorespiratory System</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organ</strong></td>
</tr>
<tr>
<td><strong>Receptor</strong></td>
</tr>
<tr>
<td>Heart 1. Sinoatrial</td>
</tr>
<tr>
<td>2. Atrioventricular node</td>
</tr>
<tr>
<td>3. Atria</td>
</tr>
<tr>
<td>4. Ventricles</td>
</tr>
<tr>
<td>Blood Vessels 1. Skin, splanchnic</td>
</tr>
<tr>
<td>2. Skeletal muscle</td>
</tr>
<tr>
<td>3. Coronary</td>
</tr>
<tr>
<td>Lungs 1. Bronchiolar smooth muscle</td>
</tr>
<tr>
<td>2. Bronchiolar glands</td>
</tr>
</tbody>
</table>
**Common Drug Endings**

Table 5. Common Drug Endings

<table>
<thead>
<tr>
<th>Ending</th>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>-afil</td>
<td>5-PDE inhibitor</td>
<td>sildenafil</td>
</tr>
<tr>
<td>-ane</td>
<td>Inhaled general anesthetic</td>
<td>halothane</td>
</tr>
<tr>
<td>-azepam</td>
<td>Benzodiazepine</td>
<td>lorazepam</td>
</tr>
<tr>
<td>-azole</td>
<td>Antifungal</td>
<td>ketoconazole</td>
</tr>
<tr>
<td>-caine</td>
<td>Local anesthetic</td>
<td>lidocaine</td>
</tr>
<tr>
<td>-olol</td>
<td>β-blocker</td>
<td>propranolol</td>
</tr>
<tr>
<td>-prazole</td>
<td>Proton pump inhibitor</td>
<td>omeprazole</td>
</tr>
<tr>
<td>-prii</td>
<td>ACE inhibitor</td>
<td>captopril</td>
</tr>
<tr>
<td>-sartan</td>
<td>ARB</td>
<td>candesartan</td>
</tr>
<tr>
<td>-statin</td>
<td>HMG-CoA inhibitor</td>
<td>atorvastatin</td>
</tr>
<tr>
<td>-terol</td>
<td>β2 agonist</td>
<td>albuterol</td>
</tr>
<tr>
<td>-tidine</td>
<td>H2 antagonist</td>
<td>cimetidine</td>
</tr>
<tr>
<td>-tropin</td>
<td>Pituitary hormone</td>
<td>somatotropin</td>
</tr>
<tr>
<td>-vir</td>
<td>Antiviral</td>
<td>acyclovir</td>
</tr>
<tr>
<td>-zosin</td>
<td>α1 antagonist</td>
<td>prazosin</td>
</tr>
</tbody>
</table>

Note: Some medications are exceptions to the rule, e.g. methimazole (antithyroid)

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Skin Anatomy

Skin

- divided anatomically into epidermis, dermis, and subcutaneous tissue
- **epidermis**
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale
  - cells progress from stratum basale to stratum corneum in about 4 wk
  - stratum basale (germinativum): displays mitotic figures that give rise to keratinocytes
  - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
  - stratum granulosum: flat cells containing basophilic granules which characterize skin
  - stratum lucidum: comprised of transparent layers of packed dead cells
  - stratum corneum: flat scales of the water-resistant protein keratin
- **dermis**: comprised of connective tissue divided into two regions
  - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
  - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibers, fibroblasts, and macrophages
- **subcutaneous tissue** (subdermal)
  - consists primarily of adipose cells, larger caliber vessels, nerves and fascia

Cells in Epidermis

- keratinocytes: located in all layers of the epidermis, except the stratum corneum; connected to each other by desmosomes
- melanocytes: located in the stratum basale; keratinocyte to melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races
- Langerhans cells: important for immune surveillance
- Merkel cells: involved in touch sensation

Skin Appendages

- epidermal in origin, can extend into the dermis; includes hair, nails, and cutaneous glands

Cutaneous Glands

- **sebaceous gland**: part of pilosebaceous unit, produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
- sebum has some antifungal properties
- these glands cover entire skin surface except palms and soles
- **apocrine sweat gland**: apocrine duct empties into hair follicle above sebaceous gland
  - found in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)
- **eccrine sweat gland**: not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface

Figure 1. Histologic layers of the skin. Epidermal layer is detailed in A

Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRESS</td>
<td>drug reaction with eosinophilia and systemic symptoms</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>EM</td>
<td>erythema multiforme</td>
</tr>
<tr>
<td>Fe</td>
<td>iron</td>
</tr>
<tr>
<td>FTA-ABS</td>
<td>fluorescent treponemal antibody-absorption</td>
</tr>
<tr>
<td>GAS</td>
<td>group A β-hemolytic Streptococcus</td>
</tr>
<tr>
<td>GVHD</td>
<td>graft-vs.-host disease</td>
</tr>
<tr>
<td>HHV</td>
<td>human herpesvirus</td>
</tr>
<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
</tr>
<tr>
<td>HZV</td>
<td>herpes zoster virus</td>
</tr>
<tr>
<td>IFN</td>
<td>interferon</td>
</tr>
<tr>
<td>IFNB</td>
<td>interferon beta</td>
</tr>
<tr>
<td>LFT</td>
<td>liver function test</td>
</tr>
<tr>
<td>MADD</td>
<td>monamine oxidase inhibitor</td>
</tr>
<tr>
<td>MFR</td>
<td>malignant melanoma</td>
</tr>
<tr>
<td>MMB</td>
<td>melanoma, malignant melanoma</td>
</tr>
<tr>
<td>MRSA</td>
<td>methicillin-resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>NB-UVB</td>
<td>narrow band ultraviolet wavelength B</td>
</tr>
<tr>
<td>NCM</td>
<td>necrotic cell</td>
</tr>
<tr>
<td>Nd: Yag</td>
<td>neodymium:yttrium aluminum garnet</td>
</tr>
<tr>
<td>NNN</td>
<td>neovascular nevus</td>
</tr>
<tr>
<td>NMSS</td>
<td>nonmelanoma skin cancers</td>
</tr>
<tr>
<td>NSABP</td>
<td>National Surgical Adjuvant Breast and Bowel Project</td>
</tr>
<tr>
<td>OCP</td>
<td>oral contraceptive pill</td>
</tr>
<tr>
<td>OTC</td>
<td>over-the-counter</td>
</tr>
<tr>
<td>PASA</td>
<td>para-amino salicylic acid</td>
</tr>
<tr>
<td>PASI</td>
<td>Psoriasis Area and Severity Index</td>
</tr>
<tr>
<td>PDD</td>
<td>purified protein derivative</td>
</tr>
<tr>
<td>PUA</td>
<td>psoralen and tetracycline</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>SCC</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>SHBG</td>
<td>sex hormone-binding globulin</td>
</tr>
<tr>
<td>SJS</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SPF</td>
<td>sun protection factor</td>
</tr>
<tr>
<td>SSR</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>SSSS</td>
<td>staphylococcal scalded skin syndrome</td>
</tr>
<tr>
<td>STD</td>
<td>sexually transmitted disease</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TEN</td>
<td>toxic epidermal necrolysis</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>TSH</td>
<td>thyroid stimulating hormone</td>
</tr>
<tr>
<td>UC</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>URTI</td>
<td>upper respiratory tract infection</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>VAC</td>
<td>vacuum assisted closure</td>
</tr>
<tr>
<td>VBL</td>
<td>ultraviolet light B</td>
</tr>
<tr>
<td>VUV</td>
<td>ultraviolet wavelength C</td>
</tr>
<tr>
<td>VZV</td>
<td>varicella zoster virus</td>
</tr>
</tbody>
</table>
Skin Function

- **protection**
  - due to continuous recycling and avascularity of epidermis
  - barrier to UV radiation, mechanical/chemical insults, pathogens and dehydration

- **thermal regulation**
  - insulation to maintain body temperature in cool environments via peripheral vasoconstriction, hair, and subcutaneous adipose tissue
  - dissipation of heat in warm environments via increased activity of sweat glands and increased blood flow within dermal vascular networks

- **sensation**
  - touch, pain, and temperature sensation

- **metabolic function**
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

Definitions

**Primary Lesions**

**Definition**
- a lesion that the body makes that has not been altered by trauma or manipulation and has not regressed

**Types of Primary Lesions**

- **macule**: flat lesion, size less than 5 mm; differs from surrounding skin with respect to its color only
- **patch**: used by some dermatologists to mean a large macule, and others to mean a thin plaque
- **papule**: raised lesion less than 5 mm; its substance consists of inflammatory cells, neoplastic cells or accumulations of metabolic by-products e.g. lipids
- **plaque**: raised lesion; usually greater than 2 cm; its surface is greater than its height
- **nodule**: similar to a papule but measures 5 mm-5cm. Are often deep and palpable
- **tumor**: a large nodule; > 5 cm; tumor in this context does not imply malignancy
- **vesicle**: small raised lesion that is fluid-filled, <5 mm
- **bulla**: larger vesicle; >5 mm
- **pustule**: an elevated lesion containing purulent fluid (white, grey, yellow, green)

**Specific Types of Primary Lesions**

- **cyst**: an epithelial-lined collection containing semi-solid or fluid material
- **wheal**: a special form of papule or plaque that is blanchable and transient, formed by edema in the dermis (e.g. urticaria)
- **comedones**: collection of sebum and keratin
  - open comedo (blackhead)
  - closed comedo (whitehead; differentiated from pustule)
- **petechiae**: small pinpoint extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, <3 mm in size
- **purpura**: larger than petechia, 3 mm-1 cm in size
- **ecchymoses**: larger than purpura, >1 cm in size, i.e. a “bruise”
- **telangiectasia**: dilated superficial blood vessels; blanchable

**Secondary Morphological Lesions**

**Definition**
- develop during the evolutionary process of skin disease, or created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)
- **crust**: dried fluid (serum, blood, or purulent exudate) (e.g. impetigo)
- **scale**: excess keratin (e.g. seborrheic dermatitis)
- **lichenification**: thickening of the skin and accentuation of normal skin markings (e.g. chronic atopic dermatitis)
- **fissure**: a linear slit-like cleavage of the skin
- **excoriation**: a scratch mark
- **atrophy**: histological decrease in size and number of cells or tissues, resulting in thinning or depression of the skin

### Skin Phototypes (Fitzpatrick)

<table>
<thead>
<tr>
<th>Phototype</th>
<th>Color of Skin</th>
<th>Skin’s Response to Sun Exposure (without SPF protection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>White</td>
<td>Always burns, never tans</td>
</tr>
<tr>
<td>II</td>
<td>White</td>
<td>Always burns, little tan</td>
</tr>
<tr>
<td>III</td>
<td>Pale brown</td>
<td>Slight burn, faster tan</td>
</tr>
<tr>
<td>IV</td>
<td>Brown</td>
<td>Rarely burns, dark tan</td>
</tr>
<tr>
<td>V</td>
<td>Dark brown or black</td>
<td>Never burns, dark tan</td>
</tr>
</tbody>
</table>

**Describe a Lesion with SCALDA**

**S**ize and **S**urface area

**C**olor (e.g. hyperpigmented, hypopigmented, erythematous)

**A**rrangement (e.g. solitary, linear, reticulated, grouped, herpetiform)

**L**esion morphology

**D**istribution (e.g. dermatomal, intertriginous, symmetrical/asymmetrical, follicular)

Always check hair, nails, mucous membranes and intertriginous areas

**Patch**: used by some dermatologists to mean a large macule, and others to mean a thin plaque

**Papule**: raised lesion less than 5 mm. Its substance consists of inflammatory cells, neoplastic cells or accumulations of metabolic by-products e.g. lipids
- **erosion**: a disruption of the skin involving the epidermis alone; heals without scarring
- **ulcer**: a disruption of the skin that extends into the dermis or deeper; heals with scarring
- **scar**: replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)

**Arrangement and Distribution**

- **acral**: relating to the hands and feet (e.g. hand, foot and mouth disease)
- **annular**: ring-shaped (e.g. granuloma annulare)
- **folicular**: involving hair follicles (e.g. folliculitis)
- **guttate**: lesions following a “drop-like” pattern (e.g. guttate psoriasis)
- **Koebner phenomenon**: i.e. isomorphic response, appearance of lesions at an injury site (e.g. lichen planus, psoriasis, vitiligo); an isomorphic reaction that develops in areas of trauma after the traumatic event; usually linear
- **morbiliform**: a maculopapular rash resembling measles
- **reticular**: lesions following a net-like pattern (e.g. livedo reticularis)
- **satellite**: lesions scattered outside of primary lesion (e.g. candida diaper dermatitis)
- **serpiginous**: lesions following a snake-like pattern (e.g. cutaneous larva migrans)
- **target/targetoid**: concentric ring lesions, like a dartboard (e.g. erythema multiforme). “Target” refers to lesions with 3 different zones of color and “targetoid” refers to lesions with 2 zones of color
- **other descriptive terms**: discrete, clustered, linear, confluent, , indurated
### Table 2. Cysts

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Clinical Course</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal Cyst</td>
<td>Round, yellow/flesh-colored, slow growing, mobile, firm, fluctuant, red or tumor</td>
<td>Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris. May be post-traumatic, rarely syndromic</td>
<td>Most common cutaneous cyst in youth -- mid age</td>
<td>Central punctum may rupture (foul, cheesy odor, creamy color) and produce inflammatory reaction. Increase in size and number over time, especially in pregnancy. May become inflamed or infected.</td>
</tr>
<tr>
<td>Pilomotor Cyst</td>
<td>Single or multiple, hard, variable sized nodules under the scalp, lacks central punctum</td>
<td>Thick-walled cyst lined with stratified squamous epithelium and filled with dense keratin. Idiopathic</td>
<td>2nd most common cutaneous cyst F &gt; M</td>
<td>Rupture causes pain and inflammation.</td>
</tr>
<tr>
<td>Dermoid Cyst</td>
<td>Most commonly found at lateral third of eyebrow or midline under nose</td>
<td>Rare, congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick-walled cyst filled with dense keratin.</td>
<td>Rare</td>
<td>If nasal midline, risk of extension into CNS.</td>
</tr>
<tr>
<td>Digital Mucous Cyst</td>
<td>Usually solitary, translucent; a clear gelatinous viscous fluid may be extruded</td>
<td>Cystic lesion that originates from joint or tendon sheath, called a digital mucous cyst when found on fingertip. Associated with osteoarthritis</td>
<td>Older age</td>
<td>Stable</td>
</tr>
<tr>
<td>Milium</td>
<td>1-2 mm superficial, white to yellow subepidermal papules occurring on eyelids, cheeks, and forehead</td>
<td>Small epidermal inclusion cyst, primarily arising from pluripotential cells in epidermal or adnexal epithelium.</td>
<td>Any age 40-50% of infants</td>
<td>In newborns, spontaneously resolves in first 4 wk of life</td>
</tr>
</tbody>
</table>
## Fibrous Lesions

### Dermatofibroma

**Clinical Presentation**
- button-like, firm dermal papule or nodule, skin-colored to red-brown coloring
- majority are asymptomatic but may be pruritic and/or tender
- site: legs > arms > trunk
- dimple sign: lateral compression causes dimpling of the lesion

**Pathophysiology**
- benign tumor due to fibroblast proliferation in the dermis

**Etiology**
- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibromata can be associated with SLE

**Epidemiology**
- adults, F>M

**Differential Diagnosis**
- dermatofibrosarcoma protuberans, MM, Kaposi's sarcoma, blue nevus

**Investigations**
- biopsy if diagnosis is uncertain

**Management**
- no treatment required
- excision or cryosurgery if bothersome

---

### Skin Tags

**Clinical Presentation**
- small (1-10 mm), soft, skin-colored or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

**Pathophysiology**
- benign outgrowth of skin

**Epidemiology**
- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

**Differential Diagnosis**
- pedunculated seborrheic keratosis, compound or dermal melanocytic nevus, neurofibroma, fibroepithelioma of Pinkus (rare variant of BCC)

**Management**
- excision, electrodessication, cryosurgery

---

### Keloids

**Clinical Presentation**
- firm, shiny, skin-colored or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
- extends beyond the margins of the original injury, and may continue to expand in size for years with claw-like extensions
- can be pruritic and painful
- sites: earlobes, shoulders, sternum, scapular area

**Pathophysiology**
- excessive deposition of randomly organized collagen fibers following trauma to skin
- differentiated from a hypertrophic scar which is confined to the borders of the original injury

**Epidemiology**
- most common in black patients, followed by those of Asian descent (predilection for darker skin)
- M=F, all age groups

---

**Skin Tags are also known as**
- Acrochordons
- Fibroepithelial polyp
- Soft fibromas
- Pedunculated lipofibromas
- Cutaneous papillomas

---

**Keloids vs. Hypertrophic Scars**
- **Keloids**: extend beyond margins of original injury with claw-like extensions
- **Hypertrophic Scars**: confined to original margins of injury
Management
• intralesional corticosteroid injections
• cryotherapy
• silicone compression

Hyperkeratotic and Hyperplastic Lesions

SEBORRHEIC KERATOSIS

Clinical Presentation
• well-demarcated waxy papule/plaque with classic “stuck on” appearance
• large variety in color, size and shape
• over time lesions appear more warty, greasy and pigmented
• sites: face, trunk, upper extremities (may occur at any site except palms or soles)

Pathophysiology
• very common benign epithelial tumor

Epidemiology
• unusual <30 yr old
• autosomal dominant inheritance

Differential Diagnosis
• MM (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented AK

Investigations
• biopsy only if diagnosis uncertain

Management
• none required, for cosmetics only
• cryotherapy, curettage

ACTINIC KERATOSIS (SOLAR KERATOSIS)
• see Pre-Malignant Skin Conditions, D31

KERATOACANTHOMA
• see Malignant Skin Tumors, D32

CORN

Clinical Presentation
• firm papule with a central, translucent, cone-shaped, hard keratin core
• painful with direct pressure
• sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

Pathophysiology
• localized hyperkeratosis induced by pressure on hands and feet

Epidemiology
• F>M, can be caused by chronic microtrauma

Differential Diagnosis
• tinea pedis, plantar warts

Management
• relieve pressure with padding or alternate footwear, orthotics
• paring, curettage

Corns vs. Warts vs. Calluses
• Corns have a whitish yellow central translucent keratinous core; painful with direct pressure
• Warts bleed with paring and have a black speckled central appearance due to thrombosed capillaries; plantar warts destroy dermatoglyphics (epidermal ridges)
• Calluses have layers of yellowish keratin revealed with paring; there are no thrombosed capillaries or interruption of epidermal ridges
Pigmented Lesions and Pigmentary Disorders

Table 3. Comparison of Pigmented Lesions

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Differential Diagnosis</th>
<th>Clinical Course and Management</th>
</tr>
</thead>
</table>
| Ephelides (Freckles)      | Small (<5 mm) well-demarcated light brown macules  
Sites: sun-exposed skin | Increased melanin within basal layer of keratinocytes secondary to sun exposure | Skin phototypes II-III | Junctional nevus  
Juvenile lentigines | No treatment required. Multiply and darken with sun exposure, fade in winter. Sunscreen may prevent the appearance of new freckles |
| Solar Lentigo (Liver Spot)| Well-demarcated brown/black irregular macules  
Sites: sun-exposed skin | Small increase in number of melanocytes in the basal layer and elongation of the rete ridges due to chronic sun exposure | Most common in Caucasians >40 yr  
Skin phototypes I-II | Lentigo maligna, seborrheic keratosis, pigmented solar keratitis | Laser therapy, shave excisions, cryotherapy |
| Dermal Melanocytosis      | Congenital gray-blue solitary or grouped macules commonly on lumbosacral area  
(historically known as Mongolian Spot) | Ectopic melanocytes in dermis | 99% occurs in Asian and Aboriginal infants | Ecchymosis | Usually fades in early childhood but may persist into adulthood |
| Becker’s Nevus            | Hairy, light brown macule/patch with a papular verrucous surface  
Sites: trunk and shoulders, onset in teen years | Pigmented hamartoma with increased melanin in basal cells | M>F  
Often becomes noticeable at puberty | Hairy congenital melanocytic nevus | Hair growth follows onset of pigmentary changes. Cosmetic management (usually too large to remove) |

NEVOMELANOCYTIC NEVI
- common mole  
- be suspicious of new or changing pigmented lesions (signs of melanoma)  
- average number of moles per person: 18-40 yr  
- 3 stages of evolution
  - junctional NMN: macular; arise at dermal-epidermal junction  
  - compound NMN: papular; nevus cells move into the papillary dermis  
  - dermal NMN: skin colored papules (no longer hyperpigmented); nevus cells completely migrate into dermis

Table 4. Nevomelanocytic Nevi Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of Onset</th>
<th>Clinical Presentation</th>
<th>Histology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Birth and early infancy</td>
<td>Sharply demarcated pigmented brown plaque with regular/irregular contours and dermis (strands)</td>
<td>Nevomelanocytes in dermis (clusters) and dermis (strands)</td>
<td>Surgical excision if suspicious, due to increased risk of melanoma</td>
</tr>
</tbody>
</table>
| Acquired            | Early childhood to age 40  
Involutes by age 60 | Benign neoplasm of pigment-forming nevus cell  
Well circumscribed, round, uniformly pigmented macules/papules <1.5 cm  
Classified according to site of nevus cells | Excisional biopsy can be considered if on scalp, soles, mucous membranes, anogenital area, or if varied colors, irregular borders, pruritic, bleeding, exposed to trauma |
| Junctional          | Childhood  
Majority progress to compound nevus | Flat, irregularly bordered, uniformly tan-dark brown, sharply demarcated smooth macule | Melanocytes at dermal-epidermal junction above basement membrane | Same as above |
| Compound            | Any age  
Dermatomes, regularly bordered, smooth, round, tan-dark brown papule  
Sites: face, trunk, extremities, scalp | Melanocytes at dermal-epidermal junction; migration into dermis | Same as above |
| Dermal              | Adults  
Soft, dome-shaped, skin-colored tan/brown papules or nodules, often with telangiectasia  
Sites: face, neck | Melanocytes exclusively in dermis | Same as above |
| Atypical            | Childhood  
Variegated macule/papule/plaque  
May be large, may have regular borders or be asymmetric. May have a “fused-egg” appearance (central papule with surrounding macule)  
People with many atypical nevi and/or a family history of melanoma are at higher risk of developing a melanoma themselves | Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus  
Often with region of adjacent nests | For patients with many atypical nevi, follow with full body photographs for changes. Excisional biopsy if lesion changing or highly atypical |

*Note: Junctional, compound and dermal nevi may be congenital or acquired. They may be typical or atypical.

DDx of Hyperpigmented Macules
- Purpura (e.g. solar, ASA, anti-coagulants, steroids, hemosiderin stain)  
- Post-inflammatory  
- Melasma  
- Melanoma  
- Fixed drug eruption
MELASMA

Clinical Presentation
- even tan macules on sun-exposed areas of face (forehead, upper lip, cheeks, chin)
- usually symmetrical

Pathophysiology
- increase in number and activity of melanocytes
- associated with estrogen and progesterone
- classification determined by depth of hyperpigmentation in the skin (epidermal, dermal, mixed type)
- epidermal pigmentation is most common and can be diagnosed with Wood’s light

Epidemiology
- F>>M
- common in pregnancy (chloasma = “mask of pregnancy”) and women taking OCP and HRT
- risk factors include sun exposure and dark skin tone
- can occur with mild endocrine disturbances, antiepileptic medications and other photosensitizing drugs

Management
- bleaching cream (hydroquinone), retinoic acid, topical steroids or combination creams
- destructive modalities (chemical peels, laser treatment)
- camouflage make-up
- avoiding sun and using sunscreen are key to preventing melasma
- often fades over several months after stopping hormone treatment or delivering baby

Vitiligo

Clinical Presentation
- primary pigmentary disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply marginated white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

Pathophysiology
- acquired autoimmune destruction of melanocytes

Epidemiology
- 1% incidence, polygenic
- 30% with positive family history

Investigations
- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison’s disease,
  Type I DM
- Wood’s lamp to detect lesions: illuminates UV light onto skin to detect amelanosis (porcelain white discoloration)

Management
- sun avoidance and protection
- topical calcineurin inhibitor (e.g. tacrolimus, pimecrolimus) or topical corticosteroids
- PUVA or Narrow band UVB
- make-up
- “bleaching” normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation
Vascular Lesions

Table 5. Infantile Hemangiomas Compared to Vascular Malformations

<table>
<thead>
<tr>
<th></th>
<th>Infantile Hemangiomas</th>
<th>Vascular Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Endothelial hyperplasia</td>
<td>Congenital malformation with normal endothelial turnover</td>
</tr>
<tr>
<td><strong>Presence at Birth</strong></td>
<td>Usually postnatal</td>
<td>100% at birth (not always obvious)</td>
</tr>
<tr>
<td><strong>M:F</strong></td>
<td>1:3-5</td>
<td>1:1</td>
</tr>
<tr>
<td><strong>Natural History</strong></td>
<td>Phases:</td>
<td>Proportionate growth (can expand)</td>
</tr>
<tr>
<td></td>
<td>• Proliferating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Involuting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Involuting</td>
<td></td>
</tr>
</tbody>
</table>

HEMANGIOMAS

Clinical Presentation
- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a “bag of worms” when palpated

Pathophysiology
- benign vascular tumor
- includes: infantile hemangioma, capillary/infantile hemangioma, spider hemangioma

Table 6. Vascular Tumors

<table>
<thead>
<tr>
<th></th>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Clinical Course</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infantile Hemangioma</strong></td>
<td>Hot, firm red to blue plaques or tumors</td>
<td>Benign vascular proliferation of endothelial lining</td>
<td>Appears shortly after birth; rarely may be congenital</td>
<td>Appears shortly after birth, increases in size over months, then regresses 50% of lesions resolve spontaneously by 5 yr</td>
<td>10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis; Consider treatment if not gone by school age; propranolol; systemic corticosteroids; laser treatment; surgery</td>
</tr>
<tr>
<td><strong>Spider Angioma (Campbell Telangiectasia)</strong></td>
<td>Central red arteriole with slender branches, faintly pulsatile, blanchable</td>
<td>Associated with hyperestrogenic state (e.g. in hepatocellular disease, pregnancy, OCP)</td>
<td>Increase in number over time</td>
<td>Spider angioma will blanch when a microscope slide is applied to the centre of the lesion</td>
<td>Electrodesiccation or laser surgery; Systemic corticosteroids and IFN-α may be indicated for rapidly growing lesions</td>
</tr>
<tr>
<td><strong>Cherry Angioma (Campbell De Morgan Spot)</strong></td>
<td>Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm</td>
<td>Benign vascular neoplasm</td>
<td>&gt;30 yr old</td>
<td>Lesions do not fade in time</td>
<td>Usually no treatment needed; Laser or electrocautery for small lesions; Excision of large lesions if necessary</td>
</tr>
<tr>
<td><strong>Pyogenic Granuloma</strong></td>
<td>Bright red, dome-shaped sessile or pedunculated friable nodule Sites: fingers, lips, mouth, trunk, toes DBx: glomus tumor, nodular MM, SCC, nodular BCC</td>
<td>Rapidly developing hemangioma Proliferation of capillaries with erosion of epidermis and neutrophilia</td>
<td>&lt;30 yr old</td>
<td>Surgical excision with histologic examination</td>
<td>Electrocautery; laser; cryotherapy</td>
</tr>
</tbody>
</table>

VASCULAR MALFORMATIONS

1. Nevus Flammeus (Port-Wine Stain)

Clinical Presentation
- red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline
- most common site: nape of neck

Pathophysiology
- congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution)

Management
- laser or make-up
2. Nevus Simplex (Salmon Patch)

Clinical Presentation
- pink-red irregular patches
- midline macule on glabella known as "Angel Kiss"; on nuchal region known as "Stork Bites"
- present in 1/3 of newborns
- majority regress spontaneously

Pathophysiology
- congenital dilation of dermal capillaries

Management
- no treatment required

Acneiform Eruptions

Acne Vulgaris/Common Acne

Clinical Presentation
- a common inflammatory pilosebaceous disease categorized with respect to severity
  - Type I: comedonal, sparse, no scarring
  - Type II: comedonal, papular, moderate ± little scarring
  - Type III: comedonal, papular, and pustular, with scarring
  - Type IV: nodulocystic acne, risk of severe scarring
- sites of predilection: face, neck, upper chest, and back

Pathophysiology
- hyperkeratinization, at the follicular ostia (opening), blocks the secretion of sebum
  (microcomedones)
- androgens stimulate sebaceous glands to produce sebum
- anaerobic diphtheroid Propionibacterium acnes bacteria contains lipase, which converts sebum
to free fatty acids and produces pro-inflammatory mediators

Epidemiology
- age of onset in puberty (10-17 yr in females, 14-19 yr in males)
- in prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital
adrenal hyperplasia)
- more severe in males than in females
- incidence decreases in adulthood
- genetic predisposition: majority of individuals with cystic acne have parent(s) with history of
severe acne

Differential Diagnosis
- folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

Table 7. Management of Acne

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoyl peroxide (BPO)</td>
<td>Bactericidal agent (targets P. acnes) and comedolytic</td>
<td>Helps prevent P. acnes resistance, is a bactericidal agent (targets P. acnes) and is comedolytic</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Comedolytic</td>
<td>Used when patients cannot tolerate a topical retinoid due to skin irritation</td>
</tr>
</tbody>
</table>

Acne Myths Debunked
- Eating greasy food and chocolate does not cause or worsen acne
- Blackheads (comedones) are black because of oxidized fatty acids, not dirt
- Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator

Acne Exacerbating Factors
- Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides,
danazol, epidermal growth factor receptor inhibitors e.g. cetuximab
- Topical agents: steroids, tars, ointments, oily cosmetics
- Mechanical pressure or occlusion, such as leaning face on hands
- Emotional stress

Accutane and Pregnancy
- Use of isotretinoin during pregnancy is associated with spontaneous abortion and major birth defects such as facial dysmorphism and cognitive impairment
- Pregnancy should be ruled out before starting isotretinoin
- Ideally, patients should use 2 forms of contraception while on isotretinoin
- Patients and their health care providers need to register with iPledge (www.ipledge.com) before isotretinoin can be prescribed and comply with mandated procedure for use of this medication

Treatment of Acne Scars
- Tretinoin creams
- Microdermabrasion for superficial scars
- Injectable fillers (collagen, hyaluronic acid)
- Fraxel laser

Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo)
Table 7. Management of Acne (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tetracycline</strong></td>
<td>Inhibits protein synthesis</td>
<td>Use caution with regard to drug interactions: do not use with isotretinoin. Sun sensitivity</td>
</tr>
<tr>
<td><strong>Oral contraceptive pills (Ortho Tri-cyclen®, Estrostep® and Yas® are FDA-approved for acne treatment)</strong></td>
<td>Norgestimate, norethindrone, drospirenone: possesses anti-androgenic, progestogenic and antigonadotrophic activity</td>
<td>After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance</td>
</tr>
<tr>
<td><strong>Spironolactone (off-label use for acne)</strong></td>
<td>Ethinyl estradiol: increases level of SHBG, reducing circulating plasma levels of androgens</td>
<td>May cause hyperkalemia at higher doses</td>
</tr>
</tbody>
</table>

**SEVERE ACNE:** Consider systemic retinoids after above treatments have failed or if significant scarring present

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Mechanism of Action</th>
<th>Notes</th>
</tr>
</thead>
</table>
| **Isotretinoin (Accutane®, Claris®)** | Retinoid that inhibits sebaceous gland function and regulates keratinization | See Table 25, D44 for full side effect profile  
Most adverse effects are temporary and will resolve when the drug is discontinued  
Baseline lipid profile (risk of hypertriglyceridemia), LFTs and β-hCG before treatment  
May transiently exacerbate acne before patient sees improvement  
Drug may be discontinued at 16-20 wk when nodule count has dropped by >70%  
A second course may be initiated after 2 mo prn  
Refractory cases may require multiple courses of isotretinoin |

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**Perioral Dermatitis**

**Clinical Presentation**
- discrete erythematous micropapules that often become confluent, forming inflammatory plaques on perioral, perinasal and periorbital skin
- commonly symmetrical, rim of sparing around vermilion border of lips

**Epidemiology**
- 15–40 yr old, occasionally in younger children
- predominantly females

**Differential Diagnosis**
- contact dermatitis, rosacea, acne vulgaris

**Management**
- avoid all topical steroids
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid

**Rosacea**

**Clinical Presentation**
- dome-shaped papules ± pustules
- flushing, non-transient erythema and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks and chin; rarely on scalp, neck and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, caffeine, spices
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration and lymphedema in the skin can develop
- phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
- ocular manifestations: blepharoconjunctivitis, keratitis, iritis

**Pathophysiology**
- unknown
Dermatitis (Eczema)

Definition
- inflammation of the skin

Clinical Presentation
- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting
- chronic dermatitis: lichenification, xerosis, fissuring

Asteatotic Dermatitis

Clinical Presentation
- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (i.e. “winter itch”) but starts in the fall
- shins predominate, looks like a “dried river bed”

Management
- skin rehydration with moisturizing routine ± mild corticosteroid creams

Atopic Dermatitis

Clinical Presentation
- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution depends on age
- inflammation, lichenification, excoriation are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with: keratosis pilaris (hyperkeratosis of hair follicles, “chicken skin”), xerosis, occupational hand dryness

Epidemiology
- frequently affects infants, children, and young adults
- almost 15% of children in developed countries under the age of 5 are affected
- associated with personal or family history of atopy (asthma, hay fever, anaphylaxis, eosinophilia)
- polygenic inheritance: one parent >60% chance for child; two parents >80% chance for child
- the earlier the onset, the more severe and persistent the disease
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

Pathophysiology
- a T-cell driven process with epidermal barrier dysfunction
Investigations
- clinical diagnosis
- consider: skin biopsy, immunoglobulin serum levels (often elevated serum IgE level), patch testing, and skin prick tests

Management
- goal: reduce signs and symptoms, prevent or reduce recurrences/flare
- better outcome (e.g. less flare-ups, modified course of disease) if diagnosis made early and treatment plan individualized
- avoid triggers of AD

- enhance barrier function of the skin
  - regular application of moisturizers
  - emollients hydrate the skin and reduce pruritus
  - twice daily application is recommended even in absence of symptoms, especially after bathing or swimming
  - bathing followed by the application of moisturizers and occlusives (e.g. petroleum jelly) promotes hydration

- anti-inflammatory therapies
  A. topical corticosteroids
    - effective, rapid symptomatic relief of acute flares
    - best applied immediately after bathing
    - control inflammation with a potent topical steroid; a milder one following resolution of acute flare
    - systemic immunosuppression may be needed in severe cases
    - flares may respond to systemic anti-staphylococcal therapy
    - side effects: skin atrophy, purpura, striae, steroid acne, perioral dermatitis, and glaucoma when used around the eyes
  B. topical immunomodulators
    - long-term management
    - calcineurin inhibitors include pimecrolimus (Elidel®), tacrolimus (Protopic®)
    - side effects: skin burning, transient irritation
    - advantages of immunomodulators over long-term corticosteroid use: rapid, sustained effect in controlling pruritus; no skin atrophy; safe for the face and neck

Complications
- infections
  - treatment of infections
    - topical mupirocin
    - oral antibiotics (e.g. cloxacillin, cephalixin) for widespread S. aureus infections

Figure 5. Atopic dermatitis treatment algorithm

Clin Dermatol 2010;28:36-44

Study: Systematic review.

Conclusions
Use of the atopy patch test (APT) is controversial:
- There is no gold standard for allergen provocation, so APT is used without comparison to another method.
- APT findings are not consistent among children with atopic dermatitis.

APT may be valuable:
- May provide diagnostic information and may aid clinical decision making regarding the use of IgE-mediated sensitizations.

Future research is needed:
- Need standardized provocation and avoidance testing to determine the clinical relevance of obtaining a positive APT result.
Contact Dermatitis

Clinical Presentation
- cutaneous inflammation caused by an external agent(s)

Table 9. Contact Dermatitis

<table>
<thead>
<tr>
<th>Mechanism of Reaction</th>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin injury to skin; non-immune mechanism</td>
<td>Cell-mediated delayed (Type IV) hypersensitivity reaction (see Rheumatology, RH2)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema, dryness, fine scale, burning</td>
<td>Erythema with a papulovesicular eruption, swelling, pruritus</td>
<td></td>
</tr>
<tr>
<td>Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majority; will occur in anyone given sufficient concentration of irritants</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmar surface of hand usually involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dorsum of hand usually involved; often discrete area of skin involvement</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examples</th>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soaps, weak alkali, detergents, organic solvents, alcohol, oils</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(See sidebar)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Many allergens are irritants, so may coincide with irritant dermatitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoidance of irritants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet compresses with Burow’s solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrier moisturizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical/oral steroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch testing to determine specific allergen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avoid allergen and its cross-reactants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wet compresses soaked in Burow’s solution (drying agent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid cream (e.g. hydrocortisone 1%, betamethasone valerate 0.05% or 0.1% cream; bid)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic steroids prn (prednisone 1 mg/kg, taper over 2 wk)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dyshidrotic Dermatitis

Clinical Presentation
- “tapioca pudding” papulovesicular dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
- acute stage often very pruritic
- secondary infection common
- lesions heal with desquamation and may lead to chronic lichenification
- sites: palms and soles ± dorsal surfaces of hands and feet

Pathophysiology
- NOT caused by hyperhidrosis (excessive sweating)
- emotional stress may precipitate the dermatitis

Management
- topical: high potency corticosteroid with plastic cling wrap occlusion to increase penetration
- intralesional triamcinolone injection
- systemic
  - prednisone in severe cases
  - antibiotics for secondary S. aureus infection

Nummular Dermatitis

Clinical Presentation
- annular, coin-shaped, pruritic, dry, scaly, erythematous plaques, can become lichenified
- often associated with atopic and dyshidrotic dermatitis
- secondary infection common

Pathophysiology
- little is known, but it is often accompanied by xerosis, which results from a dysfunction of the epidermal lipid barrier; this in turn can allow permeation of environmental agents, which can induce an allergic or irritant response

Management
- moisturization
- mid to high potency corticosteroid ointment bid
**Seborrheic Dermatitis**

**Clinical Presentation**
- greasy, erythematous, yellow, scaling, minimally elevated papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: "cradle cap"
- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

**Pathophysiology**
- possible etiologic association with *Malassezia* spp. (yeast)

**Epidemiology**
- common in infants and adolescents
- increased incidence and severity in immunocompromised patients
- in adults, can cause dandruff ( pityriasis sicca)

**Management**
- face: ketoconazole (Nizoral®) cream daily or bid + mild steroid cream daily or bid
- scalp: salicylic acid in olive oil or Derma-Smoothe FS® oil (peanut oil, mineral oil, fluocinolone acetonide 0.01%) to remove dense scales, 2% ketoconazole shampoo (Nizoral®), ciclopirox (Loprox®) shampoo, selenium sulfide (e.g. Selsun®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)

**Stasis Dermatitis**

**Clinical Presentation**
- chronic erythema, xerosis, scaling, pruritis, and brownish pigmentation in late stages
- site: lower legs

**Pathophysiology**
- chronic venous insufficiency leads to venous stasis
- surrounding soft tissue inflammation and fibrosis results

**Investigations**
- Doppler and color-coded Duplex sonography if suspicious for DVT
- culture for MRSA if there is crusting

**Management**
- compression stockings
- rest and elevate legs (above the level of the heart)
- moisturizer to treat xerosis
- mid-high potency topical corticosteroids to control inflammation

**Complications**
- ulceration (common at medial malleolus), secondary bacterial infections

**Lichen Simplex Chronicus**

**Clinical Presentation**
- well-defined plaque(s) of lichenified skin with decreased skin markings ± excoriations
- common sites: neck, scalp, lower extremeties, urogenital area
- often seen in patients with atopy

**Pathophysiology**
- skin hyperexcitable to itch, continued rubbing/scratching of skin results
- eventually lichenification occurs

**Investigations**
- if patient has generalized pruritus, rule out systemic cause: CBC with differential count, transaminases, renal and thyroid function tests
- CXR if lymphoma suspected

**Management**
- treat pruritus to break the itch-scratch cycle: antipruritics (e. g. antihistamines, topical or intralesional glucocorticoids, Unna boot)
**Lichen Planus**

**Clinical Presentation**
- acute or chronic inflammation of mucous membranes or skin, especially on flexural surfaces
- small, polygonal, pruritic, flat-topped, shiny, violet papules; resolves into hyperpigmented macules
- common sites: wrists, ankles, mucous membranes in 60% (mouth, vulva, glans), nails, scalp
- distribution: symmetrical and bilateral
- Wickham's striae: reticulate white-gray lines over surface; pathognomonic but may not be present
- mucous membrane lesions: lacy, whitish reticular network, milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging; dystrophic; pterygium formation
- scalp: scarring alopecia with perifollicular hyperkeratosis
- spontaneously resolves but may last for weeks, months or years (mouth and skin lesions)
- rarely associated with hepatitis C
- Koebner phenomenon

**Pathophysiology**
- autoimmune, antigen unknown
- lymphocyte activation leads to keratinocyte apoptosis

**Investigations**
- biopsy
- hepatitis C serology if patient has risk factors

**Management**
- topical or intralesional corticosteroids
- short courses of oral prednisone (rarely)
- phototherapy for generalized or resistant cases
- oral retinoids for erosive lichen planus in mouth
- oral metronidazole or systemic immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine)

---

**Pityriasis Rosea**

**Clinical Presentation**
- acute, self-limiting eruption characterized by red, oval plaques/patches with central scale that does not extend to edge of lesion
- long axis of lesions follows skin tension lines (i.e. Langer's Lines) parallel to ribs producing "Christmas tree" pattern on back
- varied degree of pruritus
- most start with a "herald" patch which precedes other lesions by 1-2 wk
- common sites: trunk, proximal aspects of arms and legs

**Etiology**
- suspected HHV-7 or HHV-6 reactivation

**Investigations**
- none required

**Management**
- none required; clears spontaneously in 6-12 wk
- symptomatic: topical glucocorticoids if pruritic

---

**Psoriasis**

**Classification**
1. plaque psoriasis
2. guttate psoriasis
3. erythrodermic psoriasis
4. pustular psoriasis
5. inverse psoriasis

**Pathophysiology**
- not fully understood, genetic and immunologic factors
- shortened keratinocyte cell cycle leads to Th1- and Th17-mediated inflammatory response
- Physical trauma (Koebner phenomenon)
- Infections (acute streptococcal infection precipitates guttate psoriasis)
- Stress (can be a major factor in flares)
- Drugs (rebond from stopping systemic glucocorticoids, lithium, antimalarial drugs, interferon)
- Smoking and heavy alcohol consumption
Differential Diagnosis
- AD, mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea, nummular dermatitis, lichen planus

Investigations
- biopsy (if atypical presentation, rarely needed)

1. PLAQUE PSORIASIS

Clinical Presentation
- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- often worse in winter (lack of sun and humidity)
- Auspitz sign: bleeds from minute points when scale is removed
- common sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

Management

Table 10. Topical Treatment of Psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lubricants</td>
<td>Reduce fissure formation</td>
<td>Petrolatum is effective</td>
</tr>
<tr>
<td>Salicylic acid 1-12%</td>
<td>Remove scales</td>
<td></td>
</tr>
<tr>
<td>Tar (LCC: liquor carbonis detergens)20% coal tar solution</td>
<td>Inhibits DNA synthesis, increases cell turnover</td>
<td>Poor long-term compliance</td>
</tr>
<tr>
<td>Calcipotriene/calcipotriol</td>
<td>Binds to skin 1,25-dihydroxyvitamin D3 to inhibit keratinocyte proliferation</td>
<td>Can be used on face and skin folds</td>
</tr>
<tr>
<td>Dovonex®, Siliks®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone + calcipotriene</td>
<td>See above</td>
<td>Not to be used on face and folds</td>
</tr>
<tr>
<td>Dovobet®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical Corticosteroids</td>
<td>Reduce scaling and thickness</td>
<td>Use appropriate potency steroid in different areas for degree of psoriasis</td>
</tr>
<tr>
<td>Tazarotene (Tazorac®) (gel/cream)</td>
<td>Retinoid derivative, decreased scaling</td>
<td>Use on nails</td>
</tr>
</tbody>
</table>

Table 11. Systemic Treatment of Psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse Effects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Bone marrow toxicity, hepatic cirrhosis, teratogenicity</td>
<td></td>
</tr>
<tr>
<td>PUVA</td>
<td>Pruritus, burning, cataracts, skin cancer</td>
<td></td>
</tr>
<tr>
<td>Acitretin</td>
<td>Alopecia, cheilitis, teratogenicity, epistaxis, xerosis, hypertriglyceridemia</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Renal toxicity, HTN, immunosuppression</td>
<td></td>
</tr>
<tr>
<td>UVB and “Narrow band” UVB (311-312 nm)</td>
<td>Well tolerated</td>
<td></td>
</tr>
</tbody>
</table>

Table 12. Biologics Approved in US

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Route</th>
<th>Dosing Schedule</th>
<th>Effectiveness</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (Enbrel®)*</td>
<td>SC</td>
<td>Twice weekly initially</td>
<td>++ + +</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>Adalimumab (Humira®)*</td>
<td>SC</td>
<td>Once every 2 wk</td>
<td>++ + + +</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>Infliximab (Remicade®)*</td>
<td>IV</td>
<td>~Every 2 mo</td>
<td>++ + + + +</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>Ustekinumab (Stelara®)</td>
<td>SC</td>
<td>Every 12 wk during maintenance</td>
<td>++ + + +</td>
<td>Anti-IL 12/23</td>
</tr>
</tbody>
</table>

*Can also be used to treat psoriatic arthritis

- biologics under study for treatment of psoriasis: secukinumab, brodalumab, ixekizumab, tildrakizumab, guselkumab

2. GUTTATE PSORIASIS (“DROP-LIKE”)

Clinical Presentation
- discrete, scattered salmon-pink small scaling papules
- sites: diffuse, usually on trunk and legs, sparing palms and soles
- often antecedent streptococcal pharyngitis
Management
- UVB phototherapy, sunlight, lubricants
- penicillin V or erythromycin if Group A β-hemolytic Streptococcus on throat culture

3. ERYTHRODERMIC PSORIASIS

Clinical Presentation
- generalized erythema with fine desquamative scale on surface
- associated signs and symptoms: arthralgia, severe pruritus, dehydration, electrolyte imbalance
- may have history of mild plaque psoriasis
- aggravating factors: lithium, β-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

Management
- hospitalization, bed rest, IV fluids, monitor fluids and electrolytes
- treat underlying aggravating condition, sun avoidance
- methotrexate, cyclosporine, UV, oral retinoids, biologics

4. PUSTULAR PSORIASIS

Clinical Presentation
- sudden onset of erythematous macules and papules which evolve rapidly into pustules, very painful
- can be generalized or localized to palms/soles
- patient usually has history of psoriasis; may occur with sudden withdrawal from steroid therapy

Management
- methotrexate, cyclosporine, oral retinoids, biologics
- hospitalization if generalized

5. INVERSE PSORIASIS

Clinical Presentation
- erythematous well-demarcated plaques on flexural surfaces such as axillae, inframammary folds, gluteal fold, inguinal folds
- lesions may be macerated

Management
- low potency topical corticosteroids
- topical vitamin D derivatives such as calcipotriene or calcitriol
- topical calcineurin inhibitors such as tacrolimus or pimecrolimus

6. PSORIATIC ARTHRITIS
- 5-30% of patients with psoriasis can also be suffering from psoriatic arthritis
- psoriatic patients with nail or scalp involvement are at a higher risk for developing psoriatic arthritis
- see Rheumatology, RH23

Vesicobullous Diseases

Bullous Pemphigoid

Clinical Presentation
- chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
- sometimes presents as urticarial plaques without bullae
- common sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth in 33%

Pathophysiology
- IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leads to subepidermal bullae

Epidemiology
- mean age of onset: 60-80 yr old
- possible rare association with internal malignancy
Dermatitis Herpetiformis

Clinical Presentation
- Grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging, excoriations
- Lesions grouped, bilaterally symmetrical
- Common sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

Pathophysiology
- Transglutaminase IgA deposits in the skin alone or in immune complexes leading to eosinophil and neutrophil infiltration
- 90% have HLA B8, DR3, DQWZ
- 90-100% associated with an often subclinical gluten-sensitive enteropathy (i.e. celiac disease)
- 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

Investigations
- Biopsy
- Immunofluorescence shows IgA deposits in perilesional skin

Epidemiology
- 20-60 yr old, M:F = 2:1

Pemphigus Foliaceus

An autoimmune intraepidermal blistering disease that is more superficial than pemphigus vulgaris due to antibodies against desmoglein-1, a transmembrane adhesion molecule. Appears as crusted patches, erosions and/or flaccid bullae that usually start on the trunk. Localized disease can be managed with topical steroids. Active widespread disease is treated like pemphigus vulgaris.

Pemphigus Vulgaris

Clinical Presentation
- Autoimmune blistering disease characterized by flaccid, non-pruritic intraepidermal bullae/vesicles on an erythematous or normal skin base
- May present with erosions and secondary bacterial infection
- Sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
- Nikolsky’s sign: Rubbing pressure on skin to cause bulla formation
- Asboe-Hansen sign: Pressure applied to bulla causes it to extend laterally

Pathophysiology
- IgG against epidermal desmoglein-1 and -3 leads to intraepidermal bullae

Epidemiology
- 40-60 yr old, higher prevalence in Jewish, Mediterranean, Asian populations
- Paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine

Investigations
- Immunofluorescence: shows IgG and C3 deposition intraepidermally
- Circulating serum anti-desmoglein IgG antibodies

Prognosis
- Begins with mouth lesions, followed by skin lesions
- Lesions heal with hyperpigmentation but do not scar
- May be fatal unless treated with immunosuppressive agents

Management
- Prednisone 1-2 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper ± steroid-sparing agents (e.g. azathioprine, methotrexate, gold, cyclophosphamide, cyclosporine, IVlg, mycophenolate mofetil, rituximab)
Management
• dapsone for pruritus (sulfapyridine if contraindicated or poorly tolerated)
• gluten-free diet for life

**Porphyria Cutanea Tarda**

**Clinical Presentation**
• tense vesicles/bullae in photoexposed areas subjected to trauma
• facial hypertrichosis, vesicles, and bullae in photodistribution (dorsum of hands and feet), milia, scarring
• common sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

**Pathophysiology**
• autosomal dominant or sporadic skin disorder associated with the presence of excess heme precursors
• associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

**Epidemiology**
• 30-40 yr old, M>F

**Investigations**
• urine + 5% HCl shows orange-red fluorescence under Wood's lamp (UV rays)
• 24 h urine for uroporphyrins (elevated)
• stool contains elevated coproporphyrins
• immunofluorescence shows IgE at dermal-epidermal junctions

**Management**
• discontinue aggravating substances (alcohol, estrogen therapy)
• phlebotomy to decrease body iron load
• low dose hydroxychloroquine

**Drug Eruptions**

**Drug Hypersensitivity Syndrome**
• fever followed by symmetrical bright red exanthematous eruption that may lead to internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
• classically occurs approximately 7-10 d after first exposure to the drug
• may be elevated incidence of similar reactions in siblings
• most common causes: sulfonamides, allopurinol, and anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, lamotrigine)
• 10% mortality if severe, undiagnosed, and untreated
• management: discontinue offending drug ± prednisone 0.5 mg-1 mg/kg/d, consider cyclosporine or other steroid-sparing agent in severe cases

**Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis**
• disorders with varying presence of characteristic skin lesions, blistering and mucous membrane involvement
Table 13. Comparison of Erythema Multiforme, Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Sites</th>
<th>Other Complications</th>
<th>Constitutional Symptoms</th>
<th>Etiology</th>
<th>Differential Diagnosis</th>
<th>Course and Prognosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema Multiforme</td>
<td>Macules/papules with central vesicles</td>
<td>Dorsa of hands and forearms</td>
<td>Burning and stinging</td>
<td>Infection: HSV or Mycoplasma pneumoniae</td>
<td>Lichenoid last 2 wk and heal without complications</td>
<td>Symptomatic treatment of oral antihistamines, oral antacid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Classic bull’s-eye pattern of concentric light and dark rings (typical target lesions)</td>
<td>Mucous membrane involvement (ipsilateral, tongue, buccal mucosa is possible)</td>
<td>Recurrentes Secondary bacterial infection</td>
<td></td>
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<tr>
<td></td>
<td>Bilateral and symmetric</td>
<td>Extremities with face &gt; trunk</td>
<td></td>
<td>Ur ticaria, granuloma annulare, mycosis fungoides, vasculitis</td>
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<td></td>
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<tr>
<td></td>
<td>All lesions appear within 72 h</td>
<td>Involvement of palms and soles</td>
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<tr>
<td></td>
<td>May show dermal edema</td>
<td>Lesion “fixed” for at least 7 d</td>
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<td></td>
<td>Lesion “fixed” for at least 7 d</td>
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<tr>
<td>Stevens-Johnson Syndrome</td>
<td>Cutaneous blistering with mucous membrane involvement (especially lips)</td>
<td>Prominent face and trunk involvement</td>
<td>Infection, scarring, contractures, erythema</td>
<td>Scarlet fever, phototoxic, eruption, DIC, SSSS, exfoliative dermatitis, Kawasaki disease, paraneoplastic pemphigus</td>
<td>4-6 wk course 5% mortality</td>
<td>Prolonged hospitalization, admit to burn unit if significant denudation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Atypical lesions”: red circular patch with dark purple center (i.e. targetoid)</td>
<td>Palms and soles may be involved later on &lt;10% body surface area involved by detached and detachable skin</td>
<td>Nikolsky sign</td>
<td>Occurs up to 1-3 wk after drug exposure with more rapid onset upon challenge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>“Sicker” (high fever)</td>
<td>Sheet-like epidermal detachment in &lt;10% of BSA (Nikolsky sign)</td>
<td>Prodrome 1-14 d prior to eruption with fever and flu-like illness</td>
<td>Scarlet fever, phototoxic, eruption, DIC, SSSS, exfoliative dermatitis, Kawasaki disease, paraneoplastic pemphigus</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Sheet-like epidermal detachment in &lt;10% of BSA (Nikolsky sign)</td>
<td></td>
<td>High fever &gt;101°F</td>
<td>Same as SJS</td>
<td>30% mortality due to fluid loss, reno-growth of epidemis by 3 wk, secondary infection</td>
<td>Same as SJS</td>
<td>Admit to burn unit Consider IVIg vs. cyclosporine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Same as SJS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Same as SJS</td>
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<tr>
<td>Toxic Epidermal Necrolysis</td>
<td>Mucous membrane involvement, and severe blistering</td>
<td>Nails may also shed</td>
<td>Same as SJS PLUS electrolyte imbalance, dehydration, tubular necrosis and acute kidney injury, epithelial erosions of trachea, death</td>
<td>Same as SJS</td>
<td></td>
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<tr>
<td></td>
<td>“Atypical lesions”: 50% have no target lesions</td>
<td>Diffuse erythema then necrosis and sheet-like epidermal detachment in &gt;30% of BSA</td>
<td>Predrome 1-14 d prior to eruption with fever and flu-like illness</td>
<td>Scarlet fever, phototoxic, eruption, DIC, SSSS, exfoliative dermatitis, Kawasaki disease, paraneoplastic pemphigus</td>
<td>4-6 wk course 5% mortality</td>
<td>Prolonged hospitalization, admit to burn unit if significant denudation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prodrome 1-14 d prior to eruption with fever and flu-like illness</td>
<td>Scarlet fever, phototoxic, eruption, DIC, SSSS, exfoliative dermatitis, Kawasaki disease, paraneoplastic pemphigus</td>
<td>4-6 wk course 5% mortality</td>
<td>Prolonged hospitalization, admit to burn unit if significant denudation</td>
</tr>
</tbody>
</table>

* SJS/TEN overlap is defined as the presence of 10-30% detached and detachable skin

Exanthematous Eruptions (Maculopapular Eruptions/Morbilliform)

- symmetrical, widespread, erythematous patches or plaques ± scales
- the “classic” and most common adverse drug reaction
- often starts on trunk
- may progress to generalized exfoliative dermatitis especially if the drug is continued
- most common causes: penicillin, sulfonamides, phenytoin
- management: discontinue offending drug ± oral antihistamines or topical/oral corticosteroids

Fixed Drug Eruptions

- sharply demarcated erythematous oval patches on the skin or mucous membranes
  - common sites: face, mucosa, genitalia, acral
  - recurs in same location upon subsequent exposure to the drug (fixed location)
- most common causes: antimicrobials (tetracycline, sulfonamides), anti-inflammatories, psychoactive agents (barbiturates), phenolphthalein
- management: discontinue offending drug ± prednisone 1mg/kg/d x 2 wk for generalized lesions ± potent topical corticosteroids for non-eroded lesions or antimicrobial ointment for eroded lesions

Photosensitivity Eruptions

- phototoxic reaction: “an exaggerated sunburn” confined to sun-exposed areas
- photoallergic reaction: an eczematous eruption that may spread to areas not exposed to light
- most common causes: chlorpromazine, doxycycline, thiazide diuretics, procarbazine
- management: sun protection ± topical/oral corticosteroids

Intravenous Immunoglobulin Use in Patients with Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome

Am J Clin Dermatol 2006;7:359-368

Study: Systematic review of 17 articles (retrospective cohort studies were most common, no RCTs).

Patients: Individuals with a diagnosis of SJS/TEN treated with IVIg.

Intervention: Various doses and regimens of IVIg.

Outcomes: Time to disease cessation, time to healing.

Results: Eleven of 14 TEN studies reported positive results, while three studies did not observe a statistically significant improvement. Two of three SJS studies reported positive results, with one study observing no significant difference in mortality, or speed of healing.

Conclusion: IVIg appears to have a positive impact on TEN/SJS but results cannot be statistically analyzed as a whole due to variability and inconsistency in data presented from each study. However, it is considered the gold standard treatment.
**Serum Sickness-Like Reaction**

- a symmetric drug eruption resulting in fever, arthralgia, lymphadenopathy, and skin rash (urticaria)
- usually appears 5-10 d after drug exposure
- most common causes: cefaclor in kids; bupropion (Zyban®, Wellbutrin®) in adults
- management: discontinue offending drug ± topical/oral corticosteroids

**Heritable Disorders**

**Ichthyosis Vulgaris**

**Clinical Presentation**
- generalized hyperkeratosis leading to dry skin
- “fish-scale” appearance especially on extremities with sparing of flexural creases, palms and soles

**Pathophysiology**
- genetic deficiency in filaggrin protein leads to abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

**Epidemiology**
- 1:300 incidence
- autosomal dominant inheritance
- associated with AD and keratosis pilaris

**Investigations**
- electron microscopy: keratohyalin granules

**Management**
- immersion in bath and oils followed by an emollient cream, humectant cream, or creams/oil containing urea or α- or β-hydroxy acids
- intermittent systemic retinoids for severe cases

**Neurofibromatosis (Type I; von Recklinghausen’s Disease)**

**Clinical Presentation**
- diagnostic criteria includes 2 or more of the following
  1. more than 5 café-au-lait patches >1.5 cm in an adult or more than 5 café-au-lait macules >0.5 cm in a child under age 5 yr
  2. axillary or inguinal freckling
  3. iris hamartomas (Lisch nodules)
  4. optic gliomas
  5. neurofibromas
  6. distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see Pediatrics, P88)

**Pathophysiology**
- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence/truncation of neurofibromin (a tumour suppressor gene)

**Epidemiology**
- incidence 1:3,000

**Investigations**
- Wood’s lamp examination to detect café-au-lait macules in patients with pale skin

**Management**
- refer to orthopedics, ophthalmology, plastics, and psychology for relevant management
- follow-up annually for brain tumors such as astrocytoma
- excise suspicious or painful lesions
- see Pediatrics, P88
**Epidemic Infections**

**Impetigo**

**Clinical Presentation**
- Acute purulent infection which appears micro-pustular; progresses to golden yellow “honey-crusted” lesions surrounded by erythema
- Can present with bullae
- Common sites: face, arms, legs, and buttocks

**Etiology**
- GAS, *S. aureus*, or both

**Epidemiology**
- Preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

**Differential Diagnosis**
- Infected eczema, HSV, VZV

**Investigations**
- Gram stain and culture of lesion fluid or biopsy

**Management**
- Remove crusts, use saline compresses and topical antiseptic soaks bid
- Topical antibacterials such as 2% mupirocin or fusidic acid (Canada only) tid; continue for 7-10 d after resolution
- Systemic antibiotics such as cloxacillin or cephalaxin for 7-10 d

**Dermis**

**Table 14. Comparison of Erysipelas and Cellulitis**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Clinical Presentation</th>
<th>Etiology</th>
<th>Complications</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erysipelas</strong></td>
<td>Involves upper dermis</td>
<td>GAS</td>
<td>Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy</td>
<td>DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis</td>
<td>Clinical diagnosis: rarely do skin/blood culture If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology</td>
<td>1st line: penicillin, cloxacillin or cefazolin 2nd line: clindamycin or cephalaxin If allergic to penicillin, use erythromycin</td>
</tr>
<tr>
<td><strong>Cellulitis</strong></td>
<td>Involves lower dermis/subcutaneous fat</td>
<td>GAS, <em>S. aureus</em> (large sized wounds), <em>H. influenzae</em> (peri-orbital), <em>Pasteurella multocida</em> (dog/cat bite)</td>
<td>Uncommon</td>
<td>Same as erysipelas</td>
<td>Same as erysipelas</td>
<td>1st line: cloxacillin or cefazolin/cephalexin 2nd line: erythromycin or clindamycin Children: cefuroxime If DM (foot infections): TMP/SMX and metronidazole</td>
</tr>
</tbody>
</table>
COMMON HAIR FOLLICLE INFECTIONS

Table 15. Comparison of Superficial Folliculitis, Furuncles, and Carbuncles

<table>
<thead>
<tr>
<th></th>
<th>Clinical Presentation</th>
<th>Etiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Superficial Folliculitis</strong></td>
<td></td>
<td>Normal non-pathogenic bacteria (Staphylococcus – most common; Pseudomonas – hot tub)</td>
<td>Anti-septic (Hibiclens®) Topical antibacterial (luusic acid, mupirocin, or erythromycin) Oral cloxacillin for 7-10 d</td>
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<tr>
<td><strong>Furuncles</strong> (Boils)</td>
<td></td>
<td>S. aureus</td>
<td>Incise and drain large furuncles to relieve pressure and pain If afebrile: hot wet packs, topical antibiotic If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&amp;S) Cloxacillin for 1-2 wk (especially for lesions near external auditory canal/nose, with surrounding cellulitis, and not responsive to topical therapy)</td>
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<tr>
<td><strong>Carbuncles</strong></td>
<td></td>
<td>S. aureus</td>
<td>Same as for furuncles</td>
</tr>
</tbody>
</table>

Dermatophytoses

Clinical Presentation
- infection of skin, hair and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

Pathophysiology
- digestion of keratin by dermatophytes results in scaly skin, broken hairs, crumbling nails/onycholysis

Etiology
- *Trichophyton, Microsporum, Epidermophyton* species (*Pityrosporum* is a superficial yeast and not a dermatophyte)

Investigations
- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia Nails can also be sent to pathology for PAS staining

Management
- topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type): clotrimazole, or terbinafine or ciclopirox olamine cream applied bid
- oral therapy is often indicated for onychomycosis or tinea capitis although ciclopirox nail lacquer bid x 6 mo is an option in those unable to take oral:
  - e.g. terbinafine (Lamisil® – liver toxicity, CYP2D6 inhibitor) or itraconazole (Sporanox® – CYP3A4 inhibitor, liver toxicity, CHF)

Table 16. Different Manifestations of Dermatophyte Infection

<table>
<thead>
<tr>
<th></th>
<th>Clinical Presentation</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tinea Capitis</strong></td>
<td></td>
<td>Alopeica areata, psoriasis, seborrhic dermatitis, tichillitomaria, dissecting celli of the scalp, acne keloidalis nuchae</td>
<td>Wood's light examination of hair: green fluorescence only for Microsporum infection Culture of scales/haair shaft Microscopic examination of KOH preparation of scales or hair shafts</td>
<td>Griseofulvin most common in US Terbinfine (Lamisil®) x 4 wk NB: oral agents are required to penetrate the hair root where dermatophyte resides Adjunctive antifungal shampoo or lotions may be helpful, and may prevent spread (e.g. selenium sulfide, ketoconazole, ciclopirox)</td>
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<td></td>
</tr>
<tr>
<td><strong>Tinea Corporis</strong> (Ringworm)</td>
<td></td>
<td>Nummular dermatitis, granuloma annulare, pityriasis rosea, psoriasis, seborrhic dermatitis, SLE</td>
<td>Microscopic examinations of KOH prep of scales shows hyphae Culture of scales</td>
<td>Topicals: 1% clotrimazole, 2% ketoconazole 2% miconazole, terbinafine or ciclopirox olamine cream bid for 2-4 wk Oral terbinafine, or itraconazole, or fluconazole, or ketoconazole if extensive</td>
</tr>
</tbody>
</table>
Table 16. Different Manifestations of Dermatophyte Infection (continued)

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tinea Cruris</strong> (<em>Jock Itch</em>)</td>
<td>Scaly patch/plaque with a well-defined, curved border and central clearing&lt;br&gt;Pruritic, erythematous, dry/macerated&lt;br&gt;Site: medial thigh&lt;br&gt;Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma, inverse psoriasis, seborrheic dermatitis</td>
<td>Same as for tinea corporis</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td><strong>Tinea Pedis</strong> (<em>Athlete's Foot</em>)</td>
<td>Pruritic scaling and/or maceration of the web spaces and powdery scaling of soles&lt;br&gt;Acute infection: interdigital (esp. 4th web space) red/white scales, vesicles, bullae, often with maceration&lt;br&gt;Secondary bacterial infection may occur&lt;br&gt;Chronic: non-pruritic, pink, scaling keratosis on soles and sides of feet&lt;br&gt;May present as flare-up of chronic tinea pedis&lt;br&gt;Predisposing factors: heat, humidity, occlusive footwear</td>
<td>Atopic dermatitis, contact dermatitis, dyshidrotic dermatitis, erythrasma, palmoplantar psoriasis&lt;br&gt;If only between 4th and 5th toes, soft corn</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td><strong>Tinea Manuum</strong></td>
<td>Primary fungal infection of the hand is rare; usually associated with tinea pedis&lt;br&gt;Acute: blisters at edge of red areas on hands&lt;br&gt;Chronic: single dry scaly patch</td>
<td>AD, contact dermatitis, granuloma annulare, psoriasis</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td><strong>Tinea Unguium</strong> (<em>Onychomycosis</em>)</td>
<td>Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris&lt;br&gt;Toenail infections usually precede fingernail infections&lt;br&gt;&lt;br&gt;<em>T. rubrum</em> (90% of all toenail infections)</td>
<td>Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophies, bacterial infections, chronic candidal infection&lt;br&gt;Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae&lt;br&gt;Culture of subungual scraping or nail clippings on Sabouraud’s agar&lt;br&gt;PAS stain of nail clipping by pathology</td>
<td>Terbinafine (Lamisil®) (6 wk for fingernails, 12 wk for toenails)&lt;br&gt;Itraconazole (Sporanox®) 7 d on, 3 wk off (2 pulses for fingernails, 3 pulses for toenails)&lt;br&gt;Topical: ciclopirox (Penlac®); nail lacquer (often ineffective)</td>
</tr>
</tbody>
</table>

### Parasitic Infections

**SCABIES**

**Clinical Presentation**
- characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- primary lesion: superficial linear burrows; inflammatory papules and nodules. Most common sites: finger webs, periungual and groin
- secondary lesion: small crusted papules, eczematous plaques, excoriations
- common sites: axillae, groin, buttocks, hands/feet (especially web spaces), sparing of head and neck (except in infants)

**Pathophysiology**
- scabies mite remains alive 2-3 d on clothing/sheets, however eggs can take 7 days to hatch
- incubation of 1 mo, then pruritus begins
- re-infection followed by hypersensitivity in 24 h

**Etiology**
- *Sarcoptes scabiei* (a mite)
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

**Differential Diagnosis**
- asteatotic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)

**Investigations**
- microscopic examination of root and content of burrow and mineral oil mount for mite, eggs, feces
- skin biopsy may sometimes show scabies mite

**Management**
- bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment as it is not ovicidal)
- in pregnancy permethrin is not used due to neurotoxicity. Instead topical sulfur is considered safe
- change underwear and linens; wash twice with detergent in hot water cycle then machine dry
- treat family and close contacts
- pruritus may persist for 2 months after effective treatment due to prolonged hypersensitivity reaction
- mid potency topical steroids and antihistamines for symptom management
LICE (PEDICULOSIS)

Clinical Presentation
- intensely pruritic red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs; red, excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs; excoriations
- body lice: nits and lice in seams of clothing; excoriations and secondary infection mainly on shoulders, belt-line and buttocks

Etiology
- Phthirius pubis (pubic), Pediculus humanus capitis (scalp), Pediculus humanus humanus (body): attaches to body hair and feeds
- can transmit infectious agents such as Bartonella quintana and Rickettsia prowazekii

Differential Diagnosis
- on scalp: bacterial infection of scalp, seborrheic dermatitis, on body: scabies

Diagnosis
- lice visible on inspection of affected area or clothing seams

Management
- permethrin 1% (Nix® cream rinse) (ovicidal) or permethrin 1% (RC & Cor®, Kwellada-P® shampoo)
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 d after first treatment
- shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle then machine dry
- treat sexual contacts in case of pubic lice

BED BUGS (HEMIPTERA)

Clinical Presentation
- burning wheals, turning to firm papules, often in groups of three – “breakfast, lunch and dinner” – in areas with easy access (face, neck, arms, legs, hands)

Etiology
- caused by Cimex lectularius, a small insect that feeds mainly at night (hide in crevices in walls and furniture during the day)

Differential Diagnosis
- dermatitis herpetiformis, drug eruptions, eczema, other insect bites, scabies

Investigations
- none required, but lesional biopsy can confirm insect bite reaction

Management
- professional fumigation
- topical steroids and oral H1-antagonists for symptomatic relief
- definitive treatment is removal of clutter in home and application of insecticides to walls and furniture

Viral Infections

HERPES SIMPLEX

Clinical Presentation
- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- primary
  - children and young adults
  - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - followed by antibody formation and latency of virus in dorsal nerve root ganglion
- secondary
  - recurrent form seen in adults; much more common than primary
  - prodrome: tingling, pruritus, pain
  - triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- potential complications
  - dendritic corneal ulcer
  - Erythema Multiforme
  - herpes simplex encephalitis (infants at risk)
HSV infection on atopic dermatitis causing Kaposi's varicelliform eruption (eczema herpeticum)
- two biologically and immunologically different subtypes: HSV-1 and HSV-2

**Investigations**
- Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells most common investigation although diagnosis is usually clinical
- viral culture, electron microscopy, and direct fluorecence antibody test of specimen taken from the base of a relatively new lesion
- serologic testing for antibody for current or past infection if necessary rarely performed as expensive, and high prevalence of positives

**HSV-1**
- typically “cold sores” (grouped vesicles at the mucocutaneous junction which quickly burst)
- recurrent on face, lips and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)

**Management**
- treat during prodrome to prevent vesicle formation
- topical antiviral (Zovirax®) cream, apply 5-6x/d x 4-7 d for facial/genital lesions
- oral antivirals (e.g. acyclovir, famciclovir, valacyclovir) are far more effective and have an easier dosing schedule, can be used at first sign of prodrome or if frequent outbreaks as prophylactic suppression

**HSV-2**
- sexually transmitted; incubation 2-20 d
- gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
- vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
- urethritis: watery discharge in males
- recurrent on vulva, vagina, penis for 5-7 d
- dx of genital ulcers: Candida balanitis, chancroid, syphilitic chancre

**Management**
- rupture vesicle with sterile needle if you wish to culture it
- wet dressing with aluminum subacetate solution, Burow’s compression, or betadine solution
- 1st episode: acyclovir 200 mg PO 5 times a day x 10 d
  - maintenance: acyclovir 400 mg PO bid
  - famciclovir or valacyclovir may be substituted and have better enteric absorption and less frequent dosing
- in case of herpes genitalis, look for and treat any other sexually-transmitted infections
- for active lesions in pregnancy, see Obstetrics, OB20

**HERPES ZOSTER (SHINGLES)**

**Clinical Presentation**
- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome; may be disseminated in Immunosuppressed (eg HIV, organ transplant)
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last days to weeks
- pain is can be pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly and may be permanent
- Hutchinson's sign: involvement of tip of nose suggests eye involvement
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV

**Etiology**
- caused by reactivation of VZV
- risk factors: immunosuppression, old age, occasionally associated with hematologic malignancy, stress

**Differential Diagnosis**
- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)

**Investigations**
- none required, but can do Tzanck test, direct fluorescence antibody test, or viral culture to rule out HSV

**Management**
- compress with normal saline, Burow's, or betadine solution
- analgesics (NSAIDs, amitriptyline)
- famciclovir or valacyclovir or acyclovir for 7 d; must initiate within 72 h to be of benefit; IV acyclovir for ophthalmic or disseminated Involvement
- gabapentin 300-600 mg PO tid for post-herpetic neuralgia
MOLLUSCUM CONTAGIOSUM

Clinical Presentation
- discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus (Molluscum contagiosum virus); giant verrucous forms in advanced HIV
- common sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

Etiology
- virus is spread via direct contact, auto-inoculation, sexual contact
- common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)

Investigations
- none required, however can biopsy to confirm diagnosis

Management
- topical cantharidin (a vesicant)
- cryotherapy
- curettage
- topical retinoids
- Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

WARTS (VERRUCA VULGARIS) (HUMAN PAPILLOMAVIRUS INFECTIONS)

Table 17. Different Manifestations of HPV Infection

<table>
<thead>
<tr>
<th>Verruca Vulgaris (Common Warts)</th>
<th>Verruca Plantaris (Plantar Warts) and Verruca Palmaris (Palmar Warts)</th>
<th>Verruca Planae (Flat Warts)</th>
<th>Condyloma Acuminata (Genital Warts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition and Clinical Features</td>
<td>Hyperkeratotic, elevated discrete epithelial growths with papillated surface caused by HPV</td>
<td>Hyperkeratotic, shiny, sharply margination growths</td>
<td>Skin-colored pinhead papules to soft cauliflower like masses in clusters</td>
</tr>
<tr>
<td>Differential Diagnosis</td>
<td>Paring or dermoscopic exam of surface reveals punctate, red-brown specks (thrombosed capillaries)</td>
<td>Paring of surface reveals red-brown papules (capillaries), interruption of epidermal ridges</td>
<td>Often occurs in young adults, infants, children</td>
</tr>
<tr>
<td>Distribution</td>
<td>Molluscum contagiosum, seborheic keratosis, SCC</td>
<td>May need to scrape (“pare”) lesions to differentiate wart from callus and corn (see sidebar, D7)</td>
<td>Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), Molluscum contagiosum, SCC</td>
</tr>
<tr>
<td>HPV Type</td>
<td>Located at trauma sites: fingers, hands, knees of children and teens</td>
<td>Located at pressure sites: metatarsal heads, heels, toes</td>
<td>Sites: genitalia and perianal areas</td>
</tr>
<tr>
<td></td>
<td>At least 80 types are known</td>
<td>Commonly HPV 1, 2, 4, 10</td>
<td>Commonly HPV 6 and 11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV 16, 18, 31, 33 cause cervical dysplasia, SCC and invasive cancer</td>
</tr>
</tbody>
</table>

- other viruses associated with skin changes, such as measles, roseola, fifth disease, etc.
- see Pediatrics, P57

Yeast Infections

CANDIDIASIS

Etiology
- many species of Candida (70-80% of infections are from Candida albicans)
- opportunistic infection in those with predisposing factors (e.g. trauma, malnutrition, immunodeficiency)

Candidal Paronychia
- painful red swellings of periungual skin
- management: topical agents not as effective; oral antifungals recommended

Candidal Intertrigo
- macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
- peripheral "satellite" pustules

Treatment for Warts
- **First line Therapies**: salicylic acid preparations (patches, solutions, creams, ointments), cryotherapy, topical cantharone
- **Second Line Therapies**: topical imiquimod, topical 5-fluorouracil, topical tretinoin, podophyllotoxin
- **Third Line Therapies**: curettage, cautery, surgery for non plantar warts, CO2 laser, oral cimetidine (particularly children), intralesional bleomycin (plantar warts), trichloroacetic acid, diphenycpronex
Dermatology Infections Essential Med Notes 2015

• predisposing factors: obesity, DM, systemic antibiotics, immunosuppression, malignancy
• starts as non-infectious maceration from heat, moisture and friction
• management: keep area dry, terbinafine, ciclopirox olamine, ketoconazole/clotrimazole cream bid until rash clears

PITYRIASIS (TINEA) VERSICOLOR

Clinical Presentation
• asymptomatic superficial fungal infection with finely scaling macules of various colors. In caucasian skin often red-brown to light brown, in darker skin tones often light brown to pale (thus versicolor)
• In Caucasians affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
• common sites: upper chest and back

Pathophysiology
• microbe produces carboxylic acid \( \rightarrow \) inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
• affinity for sebaceous glands; require fatty acids to survive

Etiology
• Pityrosporum ovale (Malassezia furfur)
• also associated with folliculitis and seborrheic dermatitis
• predisposing factors: summer, tropical climates, excessive sweating, Cushing’s syndrome, prolonged corticosteroid use

Investigations
• clinical diagnosis but can perform microscopic examination, KOH prep of scales for hyphae and spores

Management
• ketoconazole shampoo or cream daily
• topical terbinafine or ciclopirox olamine bid
• systemic fluconazole or itraconazole for 7 d if extensive

Sexually Transmitted Diseases

SYPHILIS

Clinical Presentation
• characterized initially by a painless ulcer (chancre)
• following inoculation, systemic infection with secondary and tertiary stages

Etiology
• Treponema pallidum
• transmitted sexually, congenitally, or rarely by transfusion

Table 18. Stages of Syphilis

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Syphilis</strong></td>
<td>CANNOT be based on clinical presentation alone</td>
<td>Penicillin G, 2.4 million units IM, single dose</td>
</tr>
<tr>
<td>Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scaly serous exudate</td>
<td>VDRL negative – repeat weekly for 1 mo</td>
<td>Notify public health authorities</td>
</tr>
<tr>
<td>Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-6 wk; chancre may also develop on lips or anus</td>
<td>Fluorescent treponemal antibody-syphilis (FTA-ABS) test has greater sensitivity and may detect disease earlier in course</td>
<td></td>
</tr>
<tr>
<td>Regional non-tender lymphadenopathy appears &lt;1 wk after onset of chancre</td>
<td>Dark field examination – spirochete in chancre fluid or lymph node aspirate</td>
<td></td>
</tr>
<tr>
<td>DDx: chancroid (painful), HSV (multiple lesions)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Syphilis</strong></td>
<td>VDRL positive</td>
<td>As for primary syphilis</td>
</tr>
<tr>
<td>Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre)</td>
<td>FTA-ABS +ve; –ve after 1 yr following appearance of chancre</td>
<td></td>
</tr>
<tr>
<td>Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgias, malaise, photophobia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesions heal in 1-5 wk and may recur for 1 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 types of lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDc: phymesis rosea, gutatte psoriasis, tinea corporis, drug eruptions, lichen plano)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Condyloma lata: wart-like moist papules around genital/perianal region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Mucous patches: macerated patches mainly found in oral mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tertiary Syphilis</strong></td>
<td>As in primary syphilis, VDRL can be falsely negative</td>
<td>Treatment: penicillin G, 2.4 million units IM weekly x 3 wk</td>
</tr>
<tr>
<td>Extremely rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-7 yr after secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main skin lesion: ‘Gumma’ – a granulomatous non-tender nodule</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Oral Terbinafine (Lamisil(\( ^\text{TM} \)) is not effective because it is not secreted by sweat glands

Natural History of Untreated Syphilis
• Inoculation
• Primary syphilis (10-90 d after infection)
• Secondary syphilis (simultaneous to primary syphilis or up to 6 mo after healing of primary lesion)
• Latent syphilis
• Tertiary syphilis (2-20 yr)

Latent Syphilis
70% of untreated patients will remain in this stage for the rest of their lives and are immune to new primary infection
GONOCOCCEMIA

Clinical Presentation
- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- common sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis, and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

Etiology
- *Neisseria gonorrhoeae*

Investigations
- requires high index of clinical suspicion plays because tests are often negative
- bacterial culture of blood, joint fluid, and skin lesions
- joint fluid cell count and Gram stain

Management
- notify Public Health authorities
- screen for other STDs
- cefixime 400 mg PO (drug of choice) or ceftriaxone 125 mg IM

HSV
- see Viral Infections, D27

HPV
- see Viral Infections, D29

Pre-Malignant Skin Conditions

Actinic Keratosis (Solar Keratosis)

Clinical Presentation
- ill-defined, scaly erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

Pathophysiology
- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of AK to SCC (~1/1,000), but higher likelihood if AK is persistent

Epidemiology
- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III, rare in darker skin as melanin is protective

Differential Diagnosis
- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

Investigations
- biopsy lesions that are refractory to treatment

Management
- destructive: cryotherapy, electrodessication and curettage
- pharmacotherapy: 5-fluorouracil cream for 2-3 wk, imiquimod cream for 8-10 wk, photodynamic therapy
- excision

Types of AK
- Erythematous: typical AK lesion
- Hypertrophic: thicker, rough papule/plaque
- Cutaneous horn: firm hyperkeratotic outgrowth
- Actinic cheilitis: confluent AKs on the lip
- Pigmented: flat, tan-brown, scaly plaque
- Spreading pigmented
- Proliferative
- Conjunctival: pinguecula, pterygium
**Leukoplakia**

**Clinical Presentation**
- A morphologic term describing homogenous or speckled white plaques with sharply demarcated borders.
- Sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue.

**Pathophysiology**
- Precancerous or premalignant condition.
- Oral form is strongly associated with tobacco use and alcohol consumption, although also occurs in congenital disease e.g., dyskeratosis congenita.

**Epidemiology**
- 1-5% prevalence in the adult population after 30 yr of age; peak at age 50.
- M>F, fair-skinned.
- Most common oral mucosal premalignant lesion.

**Differential Diagnosis**
- Lichen planus, oral hairy leukoplakia, mild oral candidiasis.

**Investigations**
- Biopsy is mandatory because it is premalignant.

**Management**
- Low risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, follow-up.
- Moderate/dysplastic lesions: excision, cryotherapy.

**Malignant Skin Tumors**

**Non-Melanoma Skin Cancers**

**Basal Cell Carcinoma**

**Subtypes**
- Noduloulcerative (typical)
  - Skin-colored papule/nodule with rolled, translucent (“pearly”) telangiectatic border and depressed/eroded/ulcerated center.
- Pigmented variant
  - Flecks of pigment in translucent lesion with surface telangiectasia.
  - May mimic malignant melanoma or seborrheic keratosis clinically.
- Superficial variant
  - Flat, tan to red-brown plaque, often with scaly, pearly border and fine telangiectasia at margin.
  - Least aggressive subtype.
- Sclerosing (morpheaform) variant
  - Flesh/yellowish-colored, shiny papule/plaque with indistinct borders, indurated.

**Pathophysiology**
- Malignant proliferation of basal keratinocytes of the epidermis.
- Low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic.
- Usually due to UVB light exposure, therefore >80% on face.
- May also occur in previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin syndrome).

**Epidemiology**
- Most common malignancy in humans.
- 75% of all malignant skin tumors >40 yr, increased prevalence in the elderly.
- M>F, skin phototypes I and II, chronic cumulative sun exposure.

**Differential Diagnosis**
- Benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma.
- Malignant: nodular MM, SCC.

**Management**
- Imiquimod 5% cream (Aldara®), 5-Flurouracil (efudex) or cryotherapy is indicated for superficial BCCs on the trunk smaller than 2 cm.
• excision or electrodessication and curettage for most types of BCCs < 2 cm and not on face, not including morpheaform
• Mohs surgery: microscopically controlled, minimally invasive, stepwise excision for lesions on the face or in areas that are difficult to reconstruct or recurrent lesions
• radiotherapy used in advanced cases of BCC where surgical intervention is not an option
• life-long follow-up
• 95% cure rate if lesion <2 cm in diameter or if treated early
• vismodegib for metastatic disease

SQUAMOUS CELL CARCINOMA

Clinical Presentation
• indurated erythematous nodule/plaque with surface scale/crust ± ulceration
• more rapid enlargement than BCC
• sites: face, ears, scalp, forearms, dorsum of hands

Pathophysiology
• malignant neoplasm of keratinocytes (primarily vertical growth)
• predisposing factors include: UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar and nitrogen mustards), HPV 16, 18, immunosuppression
• may occur in previous scar (SCC more commonly than BCC)

Epidemiology
• second most common type of cutaneous neoplasm
• primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
• in organ transplant recipients SCC is most common cutaneous malignancy, with increased mortality as compared to non-immunocompromised population

Differential Diagnosis
• benign: nummular eczema, psoriasis, irritated seborrheic keratosis, wart
• malignant: keratoacanthoma, Bowen's disease, BCC

Management
• surgical excision with primary closure, skin flaps or grafting
• Mohs surgery
• lifelong follow-up (more aggressive treatment than BCC)

Prognosis
• good prognostic factors: early treatment, negative margins, and small size of lesion
• SCCs that arise from AK metastasize less frequently (~1%) than other SCCs arising de novo in old burns (2-5% of cases)
• overall control is 75% over 5 yr, 5-10% metastasize

OTHER FORMS OF SQUAMOUS CELL CARCINOMA (SCC)

BOWEN'S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)

Clinical Presentation
• sharply demarcated erythematous plaque with scale and/or crusting
• often 1-3 cm in diameter and found on the skin and mucous membranes
• evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions

Management
• same as for BCC
• biopsy required for diagnosis
• topical 5-fluorouracil (Efudex®) or imiquimod (Aldara®) used if extensive and as a tool to identify margins of poorly defined tumors
• cryosurgery
• shave excision with electrodessication and curettage

KERATOACANTHOMA

Clinical Presentation
• rapidly growing, firm, dome-shaped, erythematous or skin-colored nodule with central keratin-filled crater, resembling an erupting volcano
• may spontaneously regress within a year, leaving a scar
• sites: sun-exposed skin
Pathophysiology
- epithelial neoplasm with atypical keratinocytes in epidermis
- low grade variant of SCC

Etiology
- HPV, UV radiation, chemical carcinogens (tar, mineral oil)

Epidemiology
- >50 yr, rare <20 yr

Differential Diagnosis
- treat as SCC until proven otherwise
- hypertrophic solar keratosis, verruca vulgaris

Management
- surgical excision or saucerization (shave biopsy) followed by electrodessication of the base, treated similarly to SCC

Malignant Melanoma

Clinical Presentation
- malignant characteristics of a mole: “ABCDE” mnemonic
- sites: skin, mucous membranes, eyes, CNS

Clinical Subtypes of Malignant Melanoma
- lentigo maligna
  - malignant melanoma in situ (normal and malignant melanocytes confined to the epidermis)
  - 2-6 cm, tan/brown/black uniformly flat macule or patch with irregular borders
  - lesion grows radially and produces complex colors
  - often seen in the elderly
  - 10% evolve to lentigo maligna melanoma
- lentigo maligna melanoma (15% of all melanomas)
  - malignant melanocytes invading into the dermis
  - associated with pre-existing solar lentigo, not pre-existing nevi
  - flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  - with time, color changes from uniform brown to dark brown with black and blue
  - found on all skin surfaces, especially those often exposed to sun, such as the face and hands
- superficial spreading melanoma (60-70% of all melanomas)
  - atypical melanocytes initially spread laterally in epidermis then invade the dermis
  - irregular, indurated, enlarging plaques with red/white/blue discoloration, focal papules or nodules
  - ulcerate and bleed with growth
- nodular melanoma (30% of all melanomas)
  - atypical melanocytes that initially grow vertically with little lateral spread
  - uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
  - rapidly fatal
  - may be pink or have no color at all, this is called an amelanotic melanoma
  - “EFG” Elevated, Firm, Growing
- acrolentiginous melanoma (5% of all melanomas)
  - ill-defined dark brown, blue-black macule
  - palmar, planter, subungual skin
  - melanomas on mucous membranes have poor prognosis

Pathophysiology
- malignant neoplasm of pigment forming cells (melanocytes and nevus cells)

Epidemiology
- incidence 1/75 (Canada) 1/50 (US)
- risk factors: numerous moles, fair skin, red hair, positive personal/family history, large congenital nevi, familial dysplastic nevus syndrome, multiple dysplastic nevi
- most common sites: back (M), calves (F)
- worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

Differential Diagnosis
- benign: nevi, solar lentigo, seborrheic keratosis
- malignant: pigmented BCC

Risk Factors for Melanoma
- no SPF is a SIN
- Sun exposure
- Pigment traits (blue eyes, fair/red hair, pale complexion)
- Freckling
- Skin reaction to sunlight (increased incidence of sunburn)
- Immunosuppressive states (e.g. renal transplantation)
- Nevi (dysplastic nevi; increased number of benign melanocytic nevi)
Management

- excisional biopsy preferable, otherwise incisional biopsy as staged by depth so shave will not be adequate
- remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis, except for small lesions (removed entirely at biopsy and additional incisional biopsy if positive)
- beware of lesions that regress – tumor is usually deeper than anticipated
- high dose IFN for stage II (regional), chemotherapy (cis-platinum, BCG) and high dose IFN for stage III (distant) disease
- newer chemotherapeutic, gene therapies and vaccines starting to be used in metastatic melanoma
- radiotherapy may be used as adjunctive treatment

Table 19. American Joint Committee on Cancer Staging System Based on Breslow’s Thickness of Invasion

<table>
<thead>
<tr>
<th>Tumor Depth</th>
<th>Stage</th>
<th>Approximate 5 Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 &lt; 1.0 mm</td>
<td>Stage I T1a – T1a</td>
<td>5 yr survival 90%</td>
</tr>
<tr>
<td>T2 1.01-2.0 mm</td>
<td>Stage II T2b – T2b</td>
<td>5 yr survival 70%</td>
</tr>
<tr>
<td>T3 2.01-4.0 mm</td>
<td>Stage III any nodes</td>
<td>5 yr survival 45%</td>
</tr>
<tr>
<td>T4 &gt; 4.0 mm</td>
<td>Stage IV any mets</td>
<td>5 yr survival 10%</td>
</tr>
</tbody>
</table>

Other Cutaneous Cancers

CUTANEOUS T-CELL LYMPHOMA

Clinical Presentation

- **Mycosis fungoides** (limited superficial type)
  - characterized by erythematous patches/plaques/nodules/tumors, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation)
  - common sites include: trunk, buttocks, proximal limbs
  - mildly symptomatic, usually excellent prognosis for early disease
- **Sézary syndrome** (widespread systemic type)
  - rare variant characterized by erythroderma, lymphadenopathy, WBC >20 x 10^9/L with Sézary cells
  - associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
  - often fatal

Pathophysiology

- clonal proliferation of skin-homing CD4 T-cells

Epidemiology

- >50 yr old, M:F 2:1

Differential Diagnosis

- tinea corporis, nummular dermatitis, psoriasis, DLE, Bowen’s disease

Investigations

- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement), epidermoptropism, atypical lymphocytes and loss of CD5 and CD7 markers
- blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is Sézary)
- imaging (for systemic involvement)

Management

- **Mycosis fungoides**
  - treatment is dependent on stage of disease
  - for patch stage: topical steroids and/or PUVA, narrow band (311-313 mm), UVB (NBUVB)
  - plaque stage: steroids, topical nitrogen mustard, bexarotene, IFN, chemotherapeutic agent
- **Sézary syndrome**
  - oral retinoids and IFN
  - extra-corporeal photophoresis
  - may need radiotherapy for total skin electron beam radiation
  - may maintain on UV therapy
  - other chemotherapeutic agents
Alopecia (Hair Loss)

Hair Growth

- hair grows in a cyclic pattern that is defined in 3 stages
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and DHT; this response is genetically controlled

Non-Scarring (Non-Cicatricial) Alopecia

ANDROGENETIC ALOPECIA

Clinical Presentation
- male- or female-pattern alopecia
- males: fronto-temporal areas progressing to vertex, entire scalp may be bald
- females: widening of central part, “Christmas tree” pattern

Pathophysiology
- action of testosterone on hair follicles

Epidemiology
- males: early 20s-30s
- females: 40s-50s

Management
- minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
- spironolactone in women (anti-androgenic effects), cyproterone acetate (Diane-35®)
- finasteride (Propecia®) (5-α-reductase inhibitor) 1 mg/d in men
- hair transplant

PHYSICAL
- trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
- traumatic (e.g. tight “corn-row” braiding of hair, wearing tight pony tails, tight tying of turbans)

TELOGEN EFFLUVIOUM

Clinical Presentation
- uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle

Pathophysiology
- variety of precipitating factors (see sidebar)
- hair loss typically occurs 2-4 mo after exposure to precipitant
- regrowth occurs within a few months but may not be complete

ANAGEN EFFLUVIOUM

Clinical Presentation
- hair loss due to insult to hair follicle impairing its mitotic activity (growth stage)

Pathophysiology
- precipitated by chemotherapeutic agents (most common), other meds (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
- dose-dependent effect
- hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
- reversible effect; follicles resume normal mitotic activity few weeks after agent stopped
ALOPECIA AREATA

Clinical Presentation
- autoimmune disorder characterized by patches of complete hair loss often localized to scalp but can affect eyebrows, beard, eyelashes, etc.
- may be associated with dystrophic nail changes – fine stippling, pitting
- "exclamation mark" pattern (hairs fractured and have tapered shafts, i.e. looks like "!")
- may be associated with pernicious anemia, vitiligo, thyroid disease, Addison's disease
- spontaneous regrowth may occur within months of first attack (worse prognosis if young at age of onset and extensive loss)
- frequent recurrence often precipitated by emotional distress

Management
- generally unsatisfactory
- intralesional triamcinolone acetonide (corticosteroids) can be used for isolated patches
- UV or PUVA therapy
- immunomodulatory (diphencyprone)

Scarring (Cicatricial) Alopecia

Clinical Presentation
- irreversible loss of hair follicles with fibrosis

Etiology
- physical: radiation, burns
- infections: fungal, bacterial, TB, leprosy, viral (HZV)
- inflammatory
  - lichen planus (lichen planopilaris)
  - DLE (note that SLE can cause an aloppecia unrelated to DLE lesions which are non-scarring)
  - morphea: "coup de sable" with involvement of center of scalp
- central centrifugal cicatricial alopecia: seen in up to 40% of black women, starting at central scalp; one of most commonly diagnosed scarring alopecias, may be associated with hair care practices in this population

Investigations
- biopsy from active border

Management
- infections: treat underlying infection
- inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials, immunosuppressants, oral steroids, retinoids, thalidomide

Nails and Disorders of the Nail Apparatus

Table 20. Nail Changes in Systemic and Dermatological Conditions

<table>
<thead>
<tr>
<th>Nail Abnormality</th>
<th>Definition/Etiology</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAIL PLATE CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clubbing</td>
<td>Proximal nail plate has greater than 180 degree angle to nail fold, watchglass nails, bulbous digits</td>
<td>Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.</td>
</tr>
<tr>
<td>Koilonychia</td>
<td>Spoon shaped nails</td>
<td>Iron deficiency, malnutrition, DM</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>Separation of nail plate from nail bed</td>
<td>Psoriasis, dermatophytes, thyroid disease</td>
</tr>
<tr>
<td>Onychogryphosis</td>
<td>Hypertrophy of the nail plate and subungal hyperkeratosis</td>
<td>Poor circulation, chronic inflammation, tinea</td>
</tr>
<tr>
<td>Onychohemia</td>
<td>Subungual hematoma</td>
<td>Trauma to nail bed</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>Fungal infection of nail (e.g. dermatophyte, yeast, mold)</td>
<td>HIV, DM, peripheral arterial disease</td>
</tr>
<tr>
<td>Onychocryptosis</td>
<td>Often hallux with congenital malalignment, painful inflammation, granulation tissue</td>
<td>Tight fitting shoes, excessive nail clipping</td>
</tr>
</tbody>
</table>

| **SURFACE CHANGES** |                  |                    |
| V-shaped nicking   | Distal margin has v-shaped loss of the nail plate | Darier’s disease (follicular dyskeratosis) |
| Pterygium inv. unguium | Distal nail plate does not separate from underlying nail bed | Scleroderma |
| Pitting           | Punctate depressions that migrate distally with growth | Psoriasis (random pattern), alopecia areata (geometric, gridshaped arrangement), eczema |
| Transverse ridging | Transverse depressions often more in central portion of nail plate | Serious acute illness slows nail growth (when present in all nails = Beau’s lines), eczema, chronic paronychia, trauma |
| Transverse white lines | Bands of white discoloration | Poisons, hypoalbuminemia (Muherte’s lines) |
### Table 20. Nail Changes in Systemic and Dermatological Conditions (continued)

<table>
<thead>
<tr>
<th>Nail Abnormality</th>
<th>Definition/Etiology</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow</td>
<td>Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis, tobacco use</td>
<td></td>
</tr>
<tr>
<td>Green</td>
<td>Pseudomonas</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>Melanoma, hematoma</td>
<td></td>
</tr>
<tr>
<td>Brown</td>
<td>Nicotine use, psoriasis, poisons, longitudinal melanonychia (ethnic)</td>
<td></td>
</tr>
<tr>
<td>Splinter hemorhages</td>
<td>Extravasation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows</td>
<td>Trauma, bacterial endocarditis, blood dyscrasias, psoriasis</td>
</tr>
<tr>
<td>Oil spots</td>
<td>Brown-yellow discoloration</td>
<td>Psoriasis</td>
</tr>
<tr>
<td><strong>NAIL FOLD CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpetic whitlow</td>
<td>HSV infection of distal phalanx</td>
<td>HSV infection</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Local inflammation of the nail fold around the nail bed</td>
<td>Acute: painful infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic: constant wetting (e.g. dishwashing, thumb sucking)</td>
</tr>
<tr>
<td>Nail fold telangiectasia</td>
<td>Cuticular hemorhages, roughness, capillary changes</td>
<td>Scleroderma, SLE, dermatomyositis</td>
</tr>
<tr>
<td>Pterygium of nail fold</td>
<td>Skin overgrows nail plate</td>
<td>lichen planitis</td>
</tr>
</tbody>
</table>

### Table 21. Skin Manifestations of Internal Conditions

#### AUTOIMMUNE DISORDERS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Related Dermatoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behcet’s disease</td>
<td>Painful aphtous ulcers in oral cavity ± genital mucous membranes, erythema nodosum, acneiform papules, pathergy</td>
</tr>
<tr>
<td>Buerger’s disease</td>
<td>Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital resorptions</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Periorbital and extensor violaceous erythema, heliotrope with edema, Gottron’s papules (violaceous flat-topped papules with atrophy), periungual erythema, telangiectasia, calcinosis cutis, shawl signs (erythema and pokioderma V-sign of chest and upper back) holister sign (hips pokioderma), photosensitivity, scalp burning</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Subcutaneous nodules, stellate purura, erythema, gangrene, splinter hemorhages, lvedo reticularis, ulceration</td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Petechiae, urticaria, erythema nodosum, rheumatic nodules, evanescent rash</td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Raynaud’s, nonpitting edema, wax/y/shiny/rose atrophic skin (morphea), fingertip pitting and ulcers, cutaneous calcification, periangual telangiectasia, acrosclerosis, salt-and-pepper leuokderma</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Malar erythema, discoid rash (erythematous papule or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purura, urticarial purura, patchy/diffuse alopecia, mucosal ulcers, photosensitivity, ‘lupus hairs (fragile hairs anterior hairline), panniculitis</td>
</tr>
<tr>
<td>Crohn’s disease/UC</td>
<td>Pyoderma gangrenosum, erythema nodosum, Sweet’s syndrome</td>
</tr>
</tbody>
</table>

#### ENDOCRINE DISORDERS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Related Dermatoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease</td>
<td>Generalized hyperpigmentation or limited to skin folds, buccal mucosa and scars</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia</td>
</tr>
<tr>
<td>DM</td>
<td>Infections (e.g. boils, carbuncles, Candidiasis, S. aureus, dermatophytoes, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipodica diabeticorum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylaxis</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropathy, onycholysis</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows</td>
</tr>
</tbody>
</table>

### Raynaud’s Phenomenon DDx

- Cold Hand
  - Cryoglobulins/Cryofibrinogens
  - Obstruction/Occupational
  - Lupus erythematosus, other connective tissue disease
  - DM/Drugs
  - Hematologic problems (polycythemia, leukemia, etc)
  - Arterial problems (atherosclerosis)
  - Neurologic problems (vascular tone)
  - Disease of unknown origin (idiopathic)

### Acanthosis Nigricans
An asymptomatic dark thickened velvety hyperpigmentation of flexural skin most commonly around the neck. Associated with DM, obesity, and other endocrine disorders and malignancy. It is a cutaneous marker of tissue insulin resistance.
Table 21. Skin Manifestations of Internal Conditions (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Related Dermatoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MALIGNANCY</strong></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Peutz-Jeghers: pigmented macules on lips/oral mucosa</td>
</tr>
<tr>
<td>Cervix/anus/rectum</td>
<td>Paget’s disease: eroding scaling plaques of perineum</td>
</tr>
<tr>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Paget’s disease: eczematous and crusting lesions of breast</td>
</tr>
<tr>
<td>GI</td>
<td>Palmoplantar keratoderma: thickened skin of palms/soles</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Sipple’s syndrome: multiple mucosal neuromas</td>
</tr>
<tr>
<td>Breast/lung/ovary</td>
<td>Dermatomyositis: heliotrope erythema on eyelids and violaceous plaques over knuckles</td>
</tr>
<tr>
<td>Lymphoma/Leukemia</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s</td>
<td>Ataxia Telangiectasia: telangiectasia on pinna, bulbar conjunctiva</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>Ichthyosis: generalized scaling especially on extremities, Sweet’s syndrome</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bloom’s syndrome: butterfly erythema on face, associated with short stature</td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry’s nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice</td>
</tr>
<tr>
<td>Renal disease</td>
<td>Pruritus, pigmentation, half and half nails, perforating dermatosis, calciphylaxis</td>
</tr>
<tr>
<td>Pruritic urticaria papules and plaques of pregnancy</td>
<td>Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms and lower backs although always spares umbilicus</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Palpable purpura in cold-exposed areas, Raynaud’s, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection</td>
</tr>
</tbody>
</table>

**Pediatric Exanthems**

- see Pediatrics, P57

**Miscellaneous Lesions**

**Angioedema and Urticaria**

**Angioedema**
- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
  - onset in childhood; 80% have positive family history
  - recurrent attacks; 25% die from laryngeal edema
  - triggers: minor trauma, emotional upset, temperature changes
- types of acquired angioedema
  - acute allergic angioedema (allergens include food, drugs, contrast media, insect venom, latex)
  - non-allergic drug reaction (drugs include ACE inhibitors)
  - acquired C1 inhibitor deficiency
- treatment
  - prophylaxis with danazol or stanozolol for hereditary angioedema
  - epinephrine pen to temporize until patient reaches hospital in acute attack

**Urticaria**
- also known as “hives”
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 h
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen
- treatment with oral antihistamines in high dosages, oral steroids, immunosuppressives (mycophenolate mofetil, Imuran) or newly approved omalizumab
Table 22. Classification of Urticaria

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Urticaria</td>
<td>Drugs: especially ASA, NSAIDs</td>
</tr>
<tr>
<td>&gt;2/3 of cases</td>
<td>Foods: nuts, shellfish, eggs, fruit</td>
</tr>
<tr>
<td>&gt;6 wk and</td>
<td>Idiopathic (2/3 of patients)</td>
</tr>
<tr>
<td>Individual</td>
<td>Infection</td>
</tr>
<tr>
<td>lesions last</td>
<td>Insect stings (bees, wasps, hornets)</td>
</tr>
<tr>
<td>&lt;24 h</td>
<td>Percutaneous absorption: cosmetics, work exposures</td>
</tr>
<tr>
<td></td>
<td>Stress</td>
</tr>
<tr>
<td></td>
<td>Systemic diseases: SLE, endocrinopathy, neoplasm</td>
</tr>
<tr>
<td>Chronic</td>
<td>IgE-dependent: trigger associated</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Idiopathic (90% of chronic urticaria patients)</td>
</tr>
<tr>
<td>&lt;1/3 of cases</td>
<td>Aeroallergens</td>
</tr>
<tr>
<td>&lt;6 wk</td>
<td>Drugs (antibiotics, hormones, local anesthetics)</td>
</tr>
<tr>
<td>Individual</td>
<td>Insect stings</td>
</tr>
<tr>
<td>lesion lasts</td>
<td>Physical contact (animal saliva, plant resins, latex, metals, lotions, soap)</td>
</tr>
<tr>
<td>&lt;24 h</td>
<td>Direct mast cell release</td>
</tr>
<tr>
<td></td>
<td>Opiates, muscle relaxants, radio-contrast agents</td>
</tr>
<tr>
<td></td>
<td>Complement-mediated</td>
</tr>
<tr>
<td></td>
<td>Serum sickness, transfusion reactions</td>
</tr>
<tr>
<td></td>
<td>Infections, viral/bacterial (80% of urticaria in pediatric patients)</td>
</tr>
<tr>
<td></td>
<td>Urticarial vasculitis</td>
</tr>
<tr>
<td></td>
<td>Arachidonic acid metabolism</td>
</tr>
<tr>
<td></td>
<td>ASA, NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
</tr>
<tr>
<td></td>
<td>Dermatographism, heat, cold, cholinergic (hot shower, exercise)</td>
</tr>
<tr>
<td></td>
<td>Solar pressure, (shoulder strap, buttocks), aqueagenic (exposure to water)</td>
</tr>
<tr>
<td></td>
<td>Adrenergic (stress), heat</td>
</tr>
<tr>
<td></td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>Mastocytosis, urticaria pigmentosa</td>
</tr>
<tr>
<td></td>
<td>In non-pruritic chronic urticaria, consider Syndromes such as Schnitzer's, Muckle-Wells and Familial Cold Urticaria</td>
</tr>
</tbody>
</table>

Urticarial Vasculitis

<table>
<thead>
<tr>
<th>Individual lesions last &gt; 24 h</th>
<th>Idiopathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Often painful, less likely pruritic, heals with bruise type lesions</td>
<td>Infections</td>
</tr>
<tr>
<td>Requires biopsy</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Autoimmune diseases</td>
</tr>
<tr>
<td></td>
<td>SLE</td>
</tr>
<tr>
<td></td>
<td>Drug hypersensitivity</td>
</tr>
<tr>
<td></td>
<td>Cimetidine and diltiazem</td>
</tr>
</tbody>
</table>

Clinical Presentation
- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on extensor lower legs (typically shins) much less commonly knees, arms
- associated with arthralgia, fever, malaise

Etiology
- 40% are idiopathic
- drugs: sulfonamides, OCPs (also pregnancy), analgesics, trans retinoic acid
- infections: GAS, TB, histoplasmosis, Yersinia
- inflammation: sarcoidosis, Crohn’s > UC
- malignancy: acute leukemia, Hodgkin's lymphoma

Epidemiology
- 15-30 yr old, F:M = 3:1
- lesions last for days and spontaneously resolve in 6 wk, although some patients will have chronic recurrence secondary to underlying conditions

Investigations
- chest X-ray (to rule out chest infection and sarcoidosis)
- throat culture, ASO titre, PPD skin test

Management
- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids
- treat underlying cause
- super saturated potassium iodide with thyroid monitoring, dapsone and colchicine

DDx of Erythema Nodosum

- NODOSUMM
  - No cause (idiopathic) in 40%
  - Drugs (sulfonamides, OCP, etc.)
  - Other infections (GAS+)
  - Sarcoidosis
  - UC and Crohn’s
  - Malignancy (leukemia, Hodgkin’s lymphoma)
  - Many infections

Approach to Urticaria
- Thorough Hx and P/E
- Acute: no immediate investigations needed; consider referral for allergy testing
- Chronic: further investigations required: CBC and differential, urinalysis, ESR, TSH, LFTs to help identify underlying cause
- Vasculitic: biopsy of lesion and referral to dermatology

Mastocytosis (Urticaria Pigmentosa)
Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Darier’s sign), due to mast cell degranulation; this occurs within minutes
Pruritus

Clinical Presentation
- a sensation provoking a desire to scratch, with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

Etiology
- dermatologic – generalized
  - astematous dermatitis (“winter itch” due to dry skin)
  - pruritus of senescent skin (may not have dry skin, any time of year)
  - infestations: scabies, lice
  - drug eruptions: ASA, antidepressants, opiates
  - psychogenic states
- dermatologic – local
  - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin’s lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, Fe deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumors), non-Hodgkin’s lymphoma
  - endocrine: carcinoid, DM, hypothyroid/thyrotoxicosis
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis

Investigations
- detailed history
- complete physical, including rectal and pelvic examination
- blood work: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture and serology for parasites, if on palms with no rash check bile acids, especially in pregnancy

Management
- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- topical corticosteroid and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria
- phototherapy with UVB or PUV A
- doxepin, amitryptyline
- gabapentin, pregabalin
- naloxone
- immunosuppressive agents if severe: steroids and steroid sparing

Wounds and Ulcers
- see Plastic Surgery. PS8, PS15

Common Medications

Sunscreens and Preventative Therapy

Sunburn
- erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
- chronic UVA, UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am to 4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

Sunscreens
- under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen but by definition SPF relates ONLY to UVB absorption.
• topical chemical: absorbs UV light
  - requires application at least 15-60 min prior to exposure, should be reapplied every 2 h (more often if sweating, swimming)
  - UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
  - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
• topical physical: reflects and scatters UV light
  - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride, and melanin
  - all are effective against the UVA and UVB spectrum
  - less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
• some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

Management
• sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, topical corticosteroids)
• antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin

Topical Steroids

Table 23. Potency Ranking of Topical Steroids

<table>
<thead>
<tr>
<th>Relative potency</th>
<th>Relative strength</th>
<th>Generic name</th>
<th>Trade names</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>x1</td>
<td>hydrocortisone</td>
<td>Emo Cort®</td>
<td>Intertinginous areas, children, face, thin skin</td>
</tr>
<tr>
<td>Moderate</td>
<td>x3</td>
<td>hydrocortisone</td>
<td>Trideril®</td>
<td>Arm, leg, trunk</td>
</tr>
<tr>
<td>Potent</td>
<td>x6</td>
<td>betamethasone</td>
<td>Betnovate®</td>
<td>Body</td>
</tr>
<tr>
<td>Very Potent</td>
<td>x9</td>
<td>betamethasone</td>
<td>Diproson®</td>
<td>Palms and soles</td>
</tr>
<tr>
<td>Extremely Potent</td>
<td>x12</td>
<td>betamethasone</td>
<td>Dermovate®</td>
<td>Palms and soles or for very limited time spans to trunk</td>
</tr>
</tbody>
</table>

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption

Dermatologic Therapies

Table 24. Common Topical Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol (Dovonex®)</td>
<td>0.005% cream, ointment, scalp solution, apply bid For maintenance therapy apply OD</td>
<td>Psoriasis</td>
<td>Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk &gt;14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)</td>
</tr>
<tr>
<td>Calcitriol (vrical)</td>
<td>Ointment</td>
<td>Psoriasis</td>
<td>Burns and its use in the skin, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk &gt;14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)</td>
</tr>
<tr>
<td>Imiquimod (Aldara®)</td>
<td>5% cream applied 3x/wk Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water Max duration 16 wk</td>
<td>Genital warts Cutaneous warts AK Superficial BCC</td>
<td>Avoid natural/artificial sun exposure Local skin and application site reactions Erythema, ulceration, edema, flu-like symptoms Works best for warts on mucosal surfaces May induce inflammation and erosion</td>
</tr>
</tbody>
</table>

Vehicles

- Ointment (water in oil): hydrate, greasy
- Cream (oil in water): hydrate, variable
- Lotion (powder in water): drying, cosmesis
- Solutions (water, alcohol, propylene glycol)
- Gel (solution that melts on contact with skin, alcohol): drying

Side Effects of Topical Steroids
- Local: atrophy, perioral dermatitis, steroid acne, rosacea, contact dermatitis, tachyphylaxis (tolerance)
- Systemic: suppression of HPA axis

Body Site

<table>
<thead>
<tr>
<th>Relative Percutaneous Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm</td>
</tr>
<tr>
<td>Plantar foot</td>
</tr>
<tr>
<td>Palm</td>
</tr>
<tr>
<td>Back</td>
</tr>
<tr>
<td>Scalp</td>
</tr>
<tr>
<td>Forehead</td>
</tr>
<tr>
<td>Cheeks</td>
</tr>
<tr>
<td>Scrotum</td>
</tr>
</tbody>
</table>

Surface Area

- 30 g covers full adult body once. Children have a greater surface area/volume ratio and there are consequently greater side effects

UV Radiation

- UVA (320-400 nm): Aging
  - Penetrates skin more effectively than UVB or UVC
  - Responsible for tanning, burning, wrinkling, photoageing and premature skin aging
  - Penetrates clouds, glass and is reflected off water, snow and cement
- UVB (290-320 nm): Burning
  - Absorbed by the outer dermis
  - Is mainly responsible for burning and premature skin aging
  - Primarily responsible for BCC, SCC
  - Does not penetrate glass and is substantially absorbed by ozone
- UVC (200-290 nm)
  - Is filtered by ozone layer
### Table 24. Common Topical Therapies (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Permethrin (Kwellada® P Lotion and Nix® Dermal Cream)</strong></td>
<td>5% cream, applied once overnight to all skin areas from neck down, repeated one week later</td>
<td>Scabies (Kwellada-P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)</td>
<td>Do not use in children &lt; 2 yr old Hypersensitivity to drug, or known sensitivity to chrysanthemums Local reactions only (resolve rapidly); including burning, pruritus Low toxicity, excellent results Consider second application after 7 d</td>
</tr>
<tr>
<td><strong>Pimecrolimus (Elidel®)</strong></td>
<td>1.0% cream bid Use for as long as lesions persist and discontinue upon resolution of symptoms</td>
<td>AD (mild to moderate)</td>
<td>Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive</td>
</tr>
<tr>
<td><strong>Tacrolimus Topical (Protopic®)</strong></td>
<td>0.03% (children) or 0.1% (adults) ointment bid Continue for duration of disease PLUS 1 wk after clearing</td>
<td>AD (mild to moderate)</td>
<td>Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expensive</td>
</tr>
</tbody>
</table>

### Table 25. Common Oral Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acitretin (Soriatane®)</strong></td>
<td>25-50 mg PO OD; maximum 75 mg/d</td>
<td>Severe psoriasis Other disorders of hyperkeratinization (ichthyosis, Darier’s disease)</td>
<td>Monitoring strategies Monitor lipids, LFTs at baseline and q1-2wk until stable Contraindications Not given to women of childbearing age Drug interactions Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives May be combined with PUVA phototherapy (known as re-PUVA)</td>
</tr>
<tr>
<td><strong>Antivirals</strong></td>
<td></td>
<td></td>
<td>Side effects Headache, nausea, diarrhea, abdominal pain Reduce dose if impaired renal function</td>
</tr>
<tr>
<td>famcyclovir (Famvir®)</td>
<td>250 mg PO tid x 7-10 d (for 1st episode of genital herpes) 125 mg PO bid x 5 d (for recurrent genital herpes)</td>
<td>Chickenpox Herpes zoster Genital herpes Acute and prophylactic to reduce transmission in infected patients Herpes labialis</td>
<td></td>
</tr>
<tr>
<td>valacyclovir (Valtrex®)</td>
<td>1000 mg PO bid x 7-10 d (for recurrent genital herpes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cyclosporin (Neoral®)</strong></td>
<td>2.5-4 mg/kg/d PO divided bid Max 4 mg/kg/d After 4 wk may increase by 0.5 mg/kg/d q2wks Concomitant dose of magnesium may protect the kidneys</td>
<td>Psoriasis May also be effective in: Lichen planus EM Recalcitrant urticaria Recalcitrant AD</td>
<td>Monitoring strategies Blood pressure, renal function Contraindications Abnormal renal function, uncontrolled HTN, malignancy (except NMISC), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug Long-term effects preclude use of cyclosporin for &gt; 2 yr; discontinue earlier if possible May consider rotating therapy with other drugs to minimize adverse effects of each drug</td>
</tr>
<tr>
<td><strong>Dapsone</strong></td>
<td>50-100-150 mg PO OD tapering to 25-50 mg PO OD to as low as 50 mg 2x/wk</td>
<td>Dermatitis herpetiformis, neutrophilic dermatoses</td>
<td>Monitoring strategies Obtain G6PD levels before initiating; in the initial two wk obtain methemoglobin levels and follow the blood counts carefully for the first few months Side effects Neupathy Hemolysis (Vitamin C and E supplementation can help prevent this) Drug interactions Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major) Often a dramatic response within hours</td>
</tr>
</tbody>
</table>
Table 25. Common Oral Therapies (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isotretinoin</strong></td>
<td>0.5-1 mg/kg/d given OD, to achieve a total dose of 120 mg/kg (20-24 wk)</td>
<td>Severe nodular and/or inflammatory acne</td>
<td>Monitoring strategies</td>
</tr>
<tr>
<td>(Accutane®)</td>
<td></td>
<td>Acne conglobata</td>
<td>Baseline lipid profile and LFTs before treatment, l-hCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recalcitrant acne</td>
<td>Contraindications</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Widespread comedonal acne</td>
<td>Teratogenic – in sexually active females, 2 forms of reliable contraception necessary</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generally regarded as unsafe in lactation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Night blindness, decreased tolerance to contact lenses, dry mucous membranes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May transiently exacerbate acne, dry skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Depression, myalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not use at the same time as tetracycline or minocycline – both may cause pseudotumor cerebri</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Discontinue vitamin A supplements</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug may be discontinued at 16-20 wk when nodule count has dropped by &gt;70%; a second course may be initiated after 2 mo prn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Refractory cases may require &gt;3 courses</td>
</tr>
<tr>
<td><strong>Itraconazole</strong></td>
<td>100-400 mg PO OD, depending on infection treated</td>
<td>Onychomycosis Tinea corporis, cruris, pedis, versicolor, capitis</td>
<td>Contraindications</td>
</tr>
<tr>
<td>(Sporanox®)</td>
<td>Tinea corporis/cruris: 200 mg PO OD x 7 d</td>
<td>Tinea pedis: 200 mg PO bid x 7 d</td>
<td>CHF</td>
</tr>
<tr>
<td></td>
<td>Tinea versicolor: 200 mg PO OD x 7 d</td>
<td>Toenails with or without fingernail involvement: 200 mg PO bid x 7 d once per mo, repeated 3x</td>
<td>Side effects</td>
</tr>
<tr>
<td></td>
<td>Finger involvement only: 200 mg bid PO x 7 d once per mo, repeated 2x</td>
<td></td>
<td>Serious hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug Interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhibits CYP3A4. Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Give capsules with food, capsules must be swallowed whole</td>
</tr>
<tr>
<td><strong>Ivermectin</strong></td>
<td>200-250 µg/kg PO qweekly x 2</td>
<td>Onchocerciasis Also effective for: scabies</td>
<td>No significant serious side effects</td>
</tr>
<tr>
<td>(Mectizan®, Stromectol®)</td>
<td>Take once as directed; repeat one wk later</td>
<td></td>
<td>Efficacious</td>
</tr>
<tr>
<td><strong>Methotrexate</strong></td>
<td>10-25 mg qwk, PO, IM, or IV Max: 30 mg/qwk</td>
<td>Psoriasis AD Pemphigus foliaceus</td>
<td>Monitoring strategies</td>
</tr>
<tr>
<td>(Trexall®)</td>
<td>To minimize side effects, administer with folic acid supplementation: 1-5 mg OD</td>
<td>Lymphomatoid papulosis</td>
<td>Baseline renal, liver, and hematological studies</td>
</tr>
<tr>
<td></td>
<td>May also be effective in: cutaneous sarcoidosis</td>
<td></td>
<td>Contraindications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>May be combined with cyclosporine to allow lower doses of both drugs</td>
</tr>
<tr>
<td><strong>Minocycline</strong></td>
<td>50-100 mg PO bid Taper to 50 mg PO OD as acne lessens</td>
<td>Acne vulgaris Rosacea</td>
<td>Contraindications</td>
</tr>
<tr>
<td>(Minocin®)</td>
<td></td>
<td></td>
<td>Caution if impaired renal or liver function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not use with isotretinoin (Accutane®)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extensive; affects multiple organ systems including CNS, teeth, eyes, bones, renal, and skin (photosensitivity and blue pigmentation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug-induced lupus (check p-ANCA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alternative to tetracycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking, HTN, migraines with aura, pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Routine gynecological health maintenance should be up to date</td>
</tr>
<tr>
<td><strong>OCPs</strong></td>
<td>TriCyclen Diane 35 Alesse All combined OCPs are helpful in acne but those listed above have undergone RCTs</td>
<td>Hormonal acne (chin, jawline) Acne associated with polycystic ovarian syndrome or other endocrine abnormalities</td>
<td>Contraindications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution if impaired renal or liver function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Do not use with isotretinoin (Accutane®)</td>
</tr>
<tr>
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<td></td>
<td>Side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extensive; affects multiple organ systems including CNS, teeth, eyes, bones, renal, and skin (photosensitivity and blue pigmentation)</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Alternative to tetracycline</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking, HTN, migraines with aura, pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Routine gynecological health maintenance should be up to date</td>
</tr>
<tr>
<td><strong>Spironolactone</strong></td>
<td>50-100 mg PO OD alone or with OCPs</td>
<td>Hormonal acne (chin, jawline) Acne with endocrine abnormality</td>
<td>Contraindications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Menstrual irregularities at higher doses if not on OCPs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Breast tenderness, mild diuresis common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of hyperkalemia – counsel patients to reduce intake of potassium rich foods such as bananas</td>
</tr>
<tr>
<td><strong>Terbinafine</strong></td>
<td>250 mg PO OD x 2 wk Fingernails x 6 wk Toenails x 12 wk</td>
<td>Onychomycosis Tinea corporis, cruris, pedis, versicolor, capitis</td>
<td>Contraindications</td>
</tr>
<tr>
<td>(Lamisil®)</td>
<td>Confirm diagnosis prior to treatment</td>
<td></td>
<td>Pregnancy, chronic or active liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug interactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Potent inhibitor of CYP2D6; use with caution when also taking β-blockers, certain anti-arrhythmic agents, MAOI type B, and/or antipsychotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drug concentrates rapidly in skin, hair, and nails at levels associated with fungicidal activity</td>
</tr>
<tr>
<td><strong>Tetracycline</strong></td>
<td>250-500 mg PO bid to tid Taken 1 h before or 2 h after a meal</td>
<td>Acne vulgaris Rosacea Bullous pemphigoid</td>
<td>Contraindications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Severe renal or hepatic dysfunction</td>
</tr>
</tbody>
</table>
Reuwe AU. Stevens-Johnson syndrome and toxic epidermal necrolysis are severe variants of the same disease which differs from erythema multiforme. J Dermatol 1997;24:726-729.
Whited JD, Grichnik JM. The rational clinical examination. Does this patient have a mole or a melanoma? JAMA 1998;279:696-701.
Acronyms

AAA abdominal aortic aneurysm  
ABG arterial blood gas  
ACS acute coronary syndrome  
AED automatic external defibrillator  
AFib atrial fibrillation  
AG anion gap  
ARDS acute respiratory distress syndrome  
AVN avascular necrosis  
AVPU alert, voice, pain, unresponsive  
AXR abdominal x-ray  
Bi-PAP bi-level positive airway pressure  
BSA body surface area  
CAS Children’s Aid Society  
CPAP continuous positive airway pressure  
CPP cerebral perfusion pressure  
CSF cerebrospinal fluid  
CVA costovertebral angle  
DIC disseminated intravascular coagulation  
DKA diabetic ketoacidosis  
DRE digital rectal exam  
DVT deep vein thrombosis  
ED emergency department  
EM erythema multiforme  
ETT endotracheal tube  
FAST focused abdominal sonogram for trauma  
FFP fresh frozen plasma  
GCS Glasgow Coma Scale  
HI head injury  
ICP intracranial pressure  
ICU intensive care unit  
ICP intracranial pressure  
JVP jugular venous pressure  
LBBB left bundle branch block  
LOC level of consciousness  
LP lumbar puncture  
MAP mean arterial pressure  
MDI metered dose inhaler  
MVC motor vehicle collision  
PACOS packed red blood cells  
RBBB right bundle branch block  
RPM range of motion  
RPS rapid primary survey  
RVI rapid sequence induction  
SAH subarachnoid hemorrhage  
SCI spinal cord injury  
SJS Stevens-Johnson syndrome  
SNV sympathetic nervous system  
SSS shortness of breath  
ST EllSTEI ST elevation myocardial infarction  
TBH traumatic brain injury  
TBN toxic epidermal necrolysis  
TSS toxic shock syndrome  
U/L/L urinalysis  
U/S ultrasound  
U/S urinalysis  
VBG venous blood gas  
VEF venicular fibrillation  
VEO venous thrombembolism  
VIE venous thrombembolism  

Initial Patient Assessment/Management

1. Rapid Primary Survey

- Airway maintenance with cervical spine (C-spine) control
- Breathing and ventilation
- Circulation (pulses, hemorrhage control)
- Disability (neurological status)
- Exposure (complete) and Environment (temperature control)
- Continually reassessed during secondary survey
- **IMPORTANT**: always watch for signs of shock while doing primary survey

**A. AIRWAY**
- First priority is to secure airway
- Assume a cervical injury in every trauma patient and immobilize with collar
- Assess ability to breathe and speak
- Can change rapidly, therefore reassess frequently

**Airway Management**
- Permit adequate oxygenation and ventilation

1. **Basic Airway Management**
   - Protect the C-spine
   - Head-tilt (if C-spine injury not suspected) or jaw thrust to open the airway
   - Sweep and suction to clear mouth of foreign material

2. **Temporizing Measures**
   - Nasopharyngeal airway (if gag reflex present, i.e. conscious)
   - Oropharyngeal airway (if gag reflex absent, i.e. unconscious)
   - “Rescue” airway devices (e.g. laryngeal mask airway, Combitube®)
   - Transvascular jet ventilation through cricothyroid membrane (last resort)

3. **Definitive Airway Management**
   - ETT intubation with in-line stabilization of C-spine
     - Oropharyngeal ± RSI preferred
     - Nasotracheal may be better tolerated in conscious patient
     - Relatively contraindicated with basal skull fracture
     - Does not provide 100% protection against aspiration
   - Surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
     - Cricothyroidotomy

**Contraindications to Intubation**
- Supraglottic/glottic pathology that would preclude successful intubation
Figure 1. Approach to endotracheal intubation in an injured patient

B. BREATHING

- **Look**
  - mental status (anxiety, agitation, decreased LOC), color, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring

- **Listen**
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping

- **Feel**
  - tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

Breathing Assessment
- objective measures of respiratory function: rate, oximetry, ABG, A-a gradient

Management of Breathing
- nasal prongs → simple face mask → non-rebreather mask → CPAP/BiPAP (in order of increasing F\textsubscript{IO\textsubscript{2}})
- Venturi mask: used to precisely control O\textsubscript{2} delivery
- Bag-Valve mask and CPAP to supplement inadequate ventilation

C. CIRCULATION

Definition of Shock
- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities)

Table 1. Major Types of Shock

<table>
<thead>
<tr>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Distributive (vasodilation)</th>
<th>Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>Myocardial ischemia</td>
<td>Septic</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>External</td>
<td>Dyshytmias</td>
<td>Anaphylactic</td>
<td>Tension pneumothorax</td>
</tr>
<tr>
<td>Severe burns</td>
<td>CHF</td>
<td>Neurogenic (spinal cord injury)</td>
<td>PE</td>
</tr>
<tr>
<td>Dehydration</td>
<td>Cardiomyopathies</td>
<td>Cardiac valve problems</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>(diabetes, DKA)</td>
<td>Cardiac valve problems</td>
<td>Cardiac valve problems</td>
<td>Constrictive pericarditis</td>
</tr>
</tbody>
</table>

Clinical Evaluation
- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities, and reduced central venous pressure
- late: hypotension and altered mental status, reduced urine output

Table 2. Estimation of Degree of Hemorrhagic Shock

<table>
<thead>
<tr>
<th>Class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss</td>
<td>&lt;750 cc</td>
<td>750-1,500 cc</td>
<td>1,500-2,000 cc</td>
<td>&gt;2,000 cc</td>
</tr>
<tr>
<td>% of blood volume</td>
<td>&lt;15%</td>
<td>15-30%</td>
<td>30-40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>&gt;120</td>
<td>&gt;140</td>
</tr>
<tr>
<td>BP</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>20</td>
<td>30</td>
<td>35</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Urinary output</td>
<td>30 cc/h</td>
<td>20 cc/h</td>
<td>10 cc/h</td>
<td>None</td>
</tr>
<tr>
<td>Fluid replacement</td>
<td>Crystalloid</td>
<td>Crystalloid</td>
<td>Crystalloid + blood</td>
<td>Crystalloid + blood</td>
</tr>
</tbody>
</table>

Estimated Systolic Blood Pressure

<table>
<thead>
<tr>
<th>SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial</td>
</tr>
<tr>
<td>Femoral</td>
</tr>
<tr>
<td>Carotid</td>
</tr>
</tbody>
</table>
Management of Hemorrhagic Shock
- ABCs
- diagnose and manage underlying cause
- if bleeding externally, apply direct pressure and elevate extremities if possible
  - do not remove impaled objects as they tamponade hemorrhage
  - tourniquet as a last resort
- resuscitation
  - infuse 1-2 L of crystalloid with large bore IVs (warmed if possible)
  - if inadequate response, consider active internal bleeding (e.g. chest, abdomen, pelvis, femurs), will likely require surgical intervention
  - if severely hypotensive on arrival or if shock persists, consider pRBC transfusion
  - transfuse crossmatched (ideally) or type-specific blood if available
  - if unavailable, transfuse O-negative in children/women of childbearing age or O-positive in all others
- with significant blood loss, early transfusion of platelets and FFP may improve outcomes

D. DISABILITY
- assess LOC using GCS
- pupils
  - inequality, size, symmetry, reactivity to light
    - inequality/sluggish suggests local eye problem or lateralizing CNS lesion
    - relative afferent pupillary defect (swinging light test) – optic nerve damage
    - extraocular movements and nystagmus
    - fundoscopy (papilledema, hemorrhages)
  - reactive pupils + decreased LOC → metabolic or structural cause
  - non-reactive pupils + decreased LOC → structural cause (especially if asymmetric)

Glasgow Coma Scale
- for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
- most useful if repeated; change in GCS with time is more relevant than the absolute number
- less meaningful for metabolic coma
- patient with deteriorating GCS needs immediate attention
- prognosis based on best post-resuscitation GCS
- reported as a 3 part score: Eyes + Verbal + Motor = Total
  - if patient intubated, GCS score reported out of 10 + T (T = tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eyes Open</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously</td>
<td>Answers questions appropriately</td>
<td>5 Obey commands 8</td>
</tr>
<tr>
<td>To voice</td>
<td>Confused, disoriented</td>
<td>4 Localizes to pain 5</td>
</tr>
<tr>
<td>To pain</td>
<td>Inappropriate words</td>
<td>3 Withdraws from pain 4</td>
</tr>
<tr>
<td>No response</td>
<td>Incomprehensible sounds</td>
<td>2 Decorticate (flexion) 3</td>
</tr>
<tr>
<td>No verbal response</td>
<td></td>
<td>1 Decerebrate (extension) 2</td>
</tr>
</tbody>
</table>

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury

Unilateral, Dilated, Non-Reactive Pupil, Think:
- Focal mass lesion
- Epidural hematoma
- Subdural hematoma

E. EXPOSURE/ENVIRONMENT
- undress patient completely and assess entire body for injury; log roll to examine back
- DRE
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

2. Resuscitation
- done concurrently with primary survey
- attend to ABCs
- manage life-threatening problems as they are identified
- vital signs q5-15 min
- ECG, BP, and O₂ monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, ß-hCG, toxicology screen, cross and type
Table 4. 2010 AHA CPR Guidelines

<table>
<thead>
<tr>
<th>Step/Action</th>
<th>Adult: &gt;8 yr</th>
<th>Child: 1-8 yr</th>
<th>Infant: &lt;1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>Head tilt-chin lift</td>
<td>Abdominal thrust</td>
<td>Back slaps and chest thrusts</td>
</tr>
<tr>
<td>Breaths</td>
<td>2 breaths at 1 second/breath – stop once see chest rise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign-Body Airway Obstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compressions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression landmarks</td>
<td>In the center of the chest, between nipples</td>
<td>Just below nipple line</td>
<td></td>
</tr>
<tr>
<td>Compression method: push hard and fast, and allow for complete recoil</td>
<td>2 hands: heel of 1 hand with second hand on top</td>
<td>2 hands: heel of 1 hand with second on top, or 1 hand: heel of 1 hand only</td>
<td>2 fingers, or thumbs</td>
</tr>
<tr>
<td>Compression depth</td>
<td>At least 2 inches</td>
<td>About 1/3 to 1/2 the depth of the chest</td>
<td></td>
</tr>
<tr>
<td>Compression rate</td>
<td>100/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression-ventilation ratio</td>
<td>30 compressions to 2 ventilations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression-only CPR</td>
<td>Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defibrillation</td>
<td>Immediate defibrillation for all rescuers responding to a sudden witnessed collapse</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Compressions (5 cycles/2 min) before AED is considered if unwitnessed arrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Secondary Survey

- done after rapid primary survey problems have been addressed
- identifies major injuries or areas of concern
- full physical exam and x-rays (C-spine, chest, pelvis – required in blunt trauma, consider T-spine and L-spine)

HISTORY

- "SAMPLE": Signs and symptoms, Allergies, Medications, Past medical history, Last meal, Events related to injury

---

**FAST view: Normal**

- heart chambers
- pericardial effusion (E)

**FAST view: Free Fluid**

1. **1. Subxiphoid Pericardial Window**
- spleen (S), L kidney (K)
- free fluid (F)

2. **2. Perisplenic**
- liver (L), kidney (K)
- blood (BL)

3. **3. Hepatorenal (Morrison’s Pouch)**
- bladder (B)
- free fluid (F)


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Figure 2. Four areas of a FAST
PHYSICAL EXAM

Head and Neck
- palpation of facial bones, scalp

Chest
- inspect for midline trachea, flail segment; ≥2 rib fractures in ≥2 places; if present look for associated hemothorax, pneumothorax, and contusions
- auscultate lung fields
- palpate for subcutaneous emphysema
- CXR

Abdomen
- assess for peritonitis, abdominal distention, and evidence of intra-abdominal bleeding
- FAST or CT (if stable)
- rectal exam for GI bleed, high riding prostate and anal tone (best to do during the log roll)
- bimanual exam in females as appropriate

Musculoskeletal
- examine all extremities for swelling, deformity, contusion, tenderness, ROM
- check for pulses and sensation in all injured limbs
- log roll and palpate thoracic and lumbar spines
- palpate iliac crests and pubic symphysis, pelvic stability (lateral, AP, vertical)
- pelvic x-ray

Neurological
- GCS
- full cranial nerve exam
- alterations of rate and rhythm of breathing are signs of structural or metabolic abnormalities
  - progressive deterioration of breathing pattern implies a failing CNS
- assess spinal cord integrity
  - conscious patient: assess distal sensation and motor
  - unconscious patient: response to painful or noxious stimulus applied to extremities

Ethical Considerations

Consent to Treatment: Adults
- see Ethical, Legal, and Organizational Medicine, ELOAM5
- Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury
- AND obtaining consent is either: a) not possible, OR b) would increase risk to the patient
  - assumes that most people would want to be saved in an emergency
- any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
- exceptions to the Emergency Rule: treatment cannot be initiated if:
  - a competent patient has previously refused the same or similar treatment and there is no evidence to suggest the patient's wishes have changed
  - an advanced directive is available (e.g. do not resuscitate order)
  - NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
- if in doubt, initiate treatment
  - care can be withdrawn if necessary at a later time or if wishes are clarified by family

Consent to Treatment: Children
- treat immediately if patient is at imminent risk
- parents/guardians have the right to make treatment decisions
- if parents refuse treatment that is life-saving or will potentially alter the child's quality of life, CAS must be contacted – consent of CAS is needed to treat

Other Issues of Consent
- need consent for HIV testing, as well as for administration of blood products
- however, if delay in substitute consent for blood transfusions puts patient at risk, transfusions can be given

Duty to Report
- law may vary depending on state
- examples: gunshot wounds, potential drunk drivers, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others
Traumatology

- Epidemiology
  - Leading cause of death in patients <45 yr
  - 4th highest cause of death in North America
  - Causes more deaths in children/adolescents than all diseases combined

- Trimodal distribution of death
  - Minutes: lethal injuries, death usually at the scene
  - Early: death within 4-6 h – “golden hour” (decreased mortality with trauma care)
  - Days-weeks: death from multiple organ dysfunction, sepsis, etc.

- Injuries fall into two categories
  - Blunt (most common): MVC, pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  - Penetrating (increasing in incidence): gunshot wound, stabbing, impalement

Considerations for Traumatic Injury

- Important to know the mechanism of injury in order to anticipate traumatic injuries
- Always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- Always inquire about head injury, loss of consciousness, amnesia, vomiting, headache, and seizure activity

Table 5. Mechanisms and Considerations of Traumatic Injuries

<table>
<thead>
<tr>
<th>Mechanism of Injury</th>
<th>Special Considerations</th>
<th>Associated Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Vehicle Collision</td>
<td>Vehicle(s) involved: weight, size, speed, damage Location of patient in vehicle Use and type of seatbelt Ejection of patient from vehicle Entrapment of patient under vehicle Airbag deployment Helmet use in motorcycle collision</td>
<td>Head-on collision: head/facial, thoracic (aortic), lower extremity Lateral/T-bone collision: head, cervical spine, thoracic, abdominal, pelvic, and lower extremity Rear-end collision: hyper-extension of cervical spine (whiplash injury) Rollover</td>
</tr>
<tr>
<td>Pedestrian-Automobile Impact</td>
<td>High morbidity and mortality Vehicle speed is an important factor Site of impact on car</td>
<td>Children at increased risk of being run over (multisystem injuries) Adults tend to be struck in lower legs (lower extremity injuries), impacted against car (truncal injuries), and thrown to ground (HII)</td>
</tr>
<tr>
<td>Falls</td>
<td>1 storey = 12 ft = 3.6 m Distance of fall: 50% mortality at 4 storeys and 95% mortality at 7 storeys Landing position (vertical vs. horizontal)</td>
<td>Vertical: lower extremity, pelvic, and spine fractures; HI Horizontal: facial, upper extremity, and rib fractures; abdominal, thoracic, and HI</td>
</tr>
</tbody>
</table>

Head Trauma

- See Neurosurgery, NS29
- 60% of MVC-related deaths are due to head injury

Specific Injuries

- Fractures
  - Dx: non-contrast head CT and physical exam
  - A. Skull fractures
    - Vault fractures
      - Linear, non-depressed
        - Most common
        - Typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
      - Depressed
        - Open (associated overlying scalp laceration and torn dura, skull fracture disrupting paranasal sinuses or middle ear) vs. closed
    - Basal skull
      - Typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
      - Clinical diagnosis superior as poorly visualized on CT
  - B. Facial fractures (see Plastic Surgery, PL28)
  - Neuronal injury
■ beware of open fracture or sinus fractures (risk of infection)
■ severe facial fractures may pose risk to airway from profuse bleeding

• scalp laceration
  ■ can be a source of significant bleeding
  ■ achieve hemostasis, inspect and palpate for skull bone defects ± CT head (rule-out skull fracture)

• neuronal injury
  A. diffuse
  ■ transient alteration in mental status that may involve loss of consciousness
    • hallmark signs of concussion: confusion and amnesia, which may occur immediately after the trauma or min later
    • loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13–15, and post-traumatic amnesia must be less than 24 h
  ■ diffuse axonal injury
    • mild: coma 6–24 h, possibly lasting deficit
    • moderate: coma >24 h, little or no signs of brainstem dysfunction
    • severe: coma >24 h, frequent signs of brainstem dysfunction

B. focal injuries
  • contusions
  • intracranial hemorrhage (epidural, subdural, intracerebral)

ASSESSMENT OF BRAIN INJURY

History
• pre-hospital status
• mechanism of injury

Physical Exam
• assume C-spine injury until ruled out
• vital signs
  • shock (not likely due to isolated brain injury, except in infants)
  • Cushing’s response to increasing ICP (bradycardia, HTN, irregular respirations)
• severity of injury determined by
  1. LOC
    • GCS ≤8 intubate, any change in score of 3 or more = serious injury
    • mild TBI = 13–15, moderate = 9–12, severe = 3–8
  2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
  3. lateralizing signs (motor/sensory)
    • may become more subtle with increasing severity of injury
    • reassess frequently

Investigations
• labs: CBC, electrolytes, PT/PTT or INR/PTT, glucose, toxicology screen
• CT scan (non-contrast) to exclude intracranial mass lesions
• C-spine imaging, often with CT head and neck to exclude intracranial mass lesions

Management
• goal in ED: reduce secondary injury by avoiding hypoxia, ischemia, decreased CPP, seizure
• general
  • ABCs
  • ensure oxygen delivery to brain through intubation and prevent hypercarbia
  • maintain BP (sBP >90)
  • treat other injuries
• early neurosurgical consultation for acute and subsequent patient management
• medical management
  • seizure treatment/prophylaxis
    – benzodiazepines, phenytoin, phenobarbital
    – steroids are of no proven value
  • treat suspected raised ICP → consider if head injury with signs of increased ICP
    – raise head of stretcher 20° if patient hemodynamically stable
    – intubate and hyperventilate (100% O₂) to a pCO₂ of 30–35 mmHg
    – mannitol 1 g/kg infused as rapidly as possible (contraindicated in shock and renal failure/anuria)
    – consider paralyzing medications if agitated/high airway pressures
    – maintenance of CPP is critical (CPP = MAP - ICP)

Disposition
• neurosurgical ICU admission for severe HI
• in hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
• for minor head injury not requiring admission, provide 24 h HI protocol to competent caregiver, follow-up with neurology as even seemingly minor HI may cause lasting deficits

**Warning Signs of Severe Head Injury**
• GCS <8
• Deteriorating GCS
• Unequal pupils
• Lateralizing signs
N.B: Altered LOC is a hallmark of brain injury

**Canadian CT Head Rule**
Lancet 2001;357:1391-1396
CT Head is only required for patients with minor head injuries with any one of the following:

**High Risk** (for neurological intervention)
• GCS score <15 at 2 h after injury.
• Suspected open or depressed skull fracture.
• Any sign of basal skull fracture (hemotympanum, “racoon” eyes, CSF otorrhea/rhinorrhea, Battle’s sign).
• Vomiting ≥2 episodes.
• Age ≥65 yr.

**Medium Risk** (for brain injury on CT)
• Amnesia before impact >30 min (i.e. cannot recall events just before impact).
• Dangerous mechanism (pedestrian struck by motor vehicle, occupant ejected from motor vehicle, fall from height >3 feet or five stairs).

Minor head injury is defined as witnessed loss of consciousness, definite amnesia, or witnessed disorientation in a patient with a GCS score of 13-15.
N.B: Canadian CT Head Rule does not apply for non-trauma cases, for GCS<13, age <16, for patients on Coumadin® and/or having a bleeding disorder, or having an obvious open skull fracture.
Mild Traumatic Brain Injury

Epidemiology
• TBI results in 1.7 million deaths, hospitalizations, and ED visits each yr (US)
• 75% are estimated to be mild TBI; remainder are moderate or severe (see Neurosurgery, NS31)
• highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features
• somatic: headache, sleep disturbance, N/V, blurred vision
• cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
• emotion and behavior: impulsivity, irritability, depression
• severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils

Etiology
• falls, MVC, and traffic accidents, struck by an object, assault, sports

Investigations
• neurological exam
• concussion recognition tool (see thinkfirst.ca)
• imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

Treatment
• close observation and follow-up; for patients at risk of intracranial complications, give appropriate discharge instructions to patient and family, watch for changes to clinical features above, and if change, return to ED
• hospitalization with normal CT (GCS <15, seizures, bleeding diathesis), or with abnormal CT
• early rehabilitation to maximize outcomes
• pharmacological management of pain, depression, headache
• follow Return to Play guidelines

Prognosis
• most recover with minimal treatment
  ▪ athletes with previous concussion are at increased risk of cumulative brain injury
• repeat TBI can lead to life-threatening cerebral edema or permanent impairment

Spine and Spinal Cord Trauma
• assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck, or back
• spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (Figure 3)
• vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
• cord may be injured despite normal C-spine x-ray (SCIWORA = spinal cord injury without radiologic abnormality)
• injuries can include: complete/incomplete transection, cord edema, spinal shock

History
• mechanism of injury, previous deficits, SAMPLE
• neck pain, paralysis/weakness, paresthesia

Physical Exam
• ABCs
• abdominal: ecchymosis, tenderness
• neurological: complete exam, including mental status
• spine: maintain neutral position, palpate C-spine; log roll, then palpate T-spine and L-spine; assess rectal tone
  ▪ when palpating, assess for tenderness, muscle spasm, bony deformities, step-off, and spinous process malalignment
• extremities: check cap refill, suspect thoracolumbar injury with calcaneal fractures

Investigations
• labs: CBC, electrolytes, Cr, glucose, coagulation profile, cross and type, toxicology screen
• imaging
  ▪ full C-spine x-ray series for trauma (AP, lateral, odontoid)
  ▪ thoracolumbar x-rays
  ▪ AP and lateral views
  ▪ indications
    ▪ patients with C-spine injury
    ▪ unconscious patients (with appropriate mechanism of injury)
    ▪ patients with neurological symptoms or findings

Investigations
• extremities: check cap refill, suspect thoracolumbar injury with calcaneal fractures

Etiology
• falls, MVC, and traffic accidents, struck by an object, assault, sports

Investigations
• neurological exam
• concussion recognition tool (see thinkfirst.ca)
• imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

Treatment
• close observation and follow-up; for patients at risk of intracranial complications, give appropriate discharge instructions to patient and family, watch for changes to clinical features above, and if change, return to ED
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• early rehabilitation to maximize outcomes
• pharmacological management of pain, depression, headache
• follow Return to Play guidelines

Prognosis
• most recover with minimal treatment
  ▪ athletes with previous concussion are at increased risk of cumulative brain injury
• repeat TBI can lead to life-threatening cerebral edema or permanent impairment

Spine and Spinal Cord Trauma
• assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck, or back
• spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (Figure 3)
• vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
• cord may be injured despite normal C-spine x-ray (SCIWORA = spinal cord injury without radiologic abnormality)
• injuries can include: complete/incomplete transection, cord edema, spinal shock

History
• mechanism of injury, previous deficits, SAMPLE
• neck pain, paralysis/weakness, paresthesia

Physical Exam
• ABCs
• abdominal: ecchymosis, tenderness
• neurological: complete exam, including mental status
• spine: maintain neutral position, palpate C-spine; log roll, then palpate T-spine and L-spine; assess rectal tone
  ▪ when palpating, assess for tenderness, muscle spasm, bony deformities, step-off, and spinous process malalignment
• extremities: check cap refill, suspect thoracolumbar injury with calcaneal fractures

Investigations
• labs: CBC, electrolytes, Cr, glucose, coagulation profile, cross and type, toxicology screen
• imaging
  ▪ full C-spine x-ray series for trauma (AP, lateral, odontoid)
  ▪ thoracolumbar x-rays
  ▪ AP and lateral views
  ▪ indications
    ▪ patients with C-spine injury
    ▪ unconscious patients (with appropriate mechanism of injury)
    ▪ patients with neurological symptoms or findings

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    ▪ patients with neurological symptoms or findings
The Canadian C-Spine Rule
JAMA 2001;286:1841-1848

For Alert (GCS Score = 15) and Stable Trauma Patients where C-Spine Injury is a Concern

1. Any high-risk factor that mandates radiography?
   - Age $\geq 65$ yr
   - Dangerous mechanism*
   - Paresthesias in extremities

   No

2. Any one low-risk factor that allows safe assessment of ROM?
   - Simple rear-end MVC†
   - Sitting position in ED
   - Ambulatory at any time
   - Delayed onset of neck pain§
   - Absence of midline C-spine tenderness

   Yes

3. Able to actively rotate neck?
   >45º left and right

   Able

No radiography

Unable

Figure 3. Approach to clearing the C-spine

Can Clear C-Spine if:
- oriented to person, place, time, and event
- no evidence of intoxication
- no posterior midline cervical tenderness
- no focal neurological deficits
- no painful distracting injuries (e.g. long bone fracture)

Management of Cord Injury
- immobilize
- evaluate ABCs
- treat shock (maintain $sBP > 100$ mmHg)
- insert NG and Foley catheter
- high dose steroids: methylprednisolone 30 mg/kg bolus, then 5.4 mg/kg/h drip, start within 6-8 h of injury (controversial and recently has less support)
- complete imaging of spine and consult spine service if available
- continually reassess high cord injuries as edema can travel up cord
- if cervical cord lesion, watch for respiratory insufficiency
  - low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact)
  - high cervical cord injury (above C4) may require intubation and ventilation
- beware of hypotension (neurogenic shock)
- treatment: warm blanket, Trendelenburg position (occasionally), volume infusion, consider vasopressors

Approach to C-Spine X-Rays
- 3-view C-spine series is the screening modality of choice
  1. lateral C1-T1 ± swimmer’s view
     - lateral view is best, identifies 90-95% of injuries
  2. odontoid view (open mouth or oblique submental view)
     - examine the dens for fractures
     - if unable to rule out fracture, repeat view or consider CT or plain film tomography
     - examine lateral aspects of C1 and spacing relative to C2

- MRIs
- Flexion/extension films
- Abnormal films
- Normal films
- C-spine cleared
- MRI neurologic exam
- Abnormal films
- Remain immobilized, consult spine service
- Normal x-rays, 3 views
- 2. CT scan if:
   - Inadequate plain film survey
   - Suspicious plain film findings
   - To better delineate injuries seen on plain films
   - Any clinical suspicion of atlanto-axial subluxation
   - High clinical suspicion of injury despite normal x-ray
   - To include C1-C3 when head C1 is indicated in head trauma

- Prevertebral soft tissue swelling is only 49% sensitive for injury

Figure 4. Lines of contour on a lateral C-spine x-ray
3. AP view
   • alignment of spinous processes in the midline
   • spacing of spinous processes should be equal
   • check vertebral bodies and facet dislocations

Table 6. Interpretation of Lateral View: The ABCS

A Adequacy and Alignment
   • Must see C1 to C7-T1 junction; if not, downward traction of shoulders, swimmer’s view, bilateral supine obliques, or CT scan needed
   • Lines of contour – in children < 8 yr of age, can see physiologic subluxation of C2 on C3, and C3 on C4, but the spino-laminal line is maintained
   • Fanning of spinous processes suggests posterior ligamentous disruption
   • Widening of facet joints
   • Check atlanto-occipital joint
   • Line extending inferiorly from clivus should transect odontoid
   • Atlanto-axial articulation, widening of predental space (normal: < 3 mm in adults, < 5 mm in children) indicates injury of C1 or C2

B Bones
   • Height, width, and shape of each vertebral body
   • Pedicles, facets, and laminae should appear as one – doubling suggests rotation

C Cartilage
   • Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression

S Soft Tissues
   • Widening of retropharyngeal (normal: < 7 mm at C1-4, may be wide in children < 2 yr on expiration) or retrotracheal spaces (normal: < 22 mm at C6-T1, < 14 mm in children < 5 yr)

Sequelea of C-Spine Fractures
   • see Neurosurgery, NS32
   • acute phase of SCI
     • spinal shock: absence of all voluntary and reflex activity below level of injury
       • decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
     • neurogenic shock: loss of vasomotor tone, SNS tone
       • watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
       • occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
       • provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
   • chronic phase of SCI
     • autonomic dysreflexia: in patients with an SCI at level T6 or above
       • signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
       • common triggers
         – GU causes: bladder distention, urinary tract infection, and kidney stones
         – GI causes: fecal impaction or bowel distension
       • treatment: monitoring and controlling BP, prior to addressing causative issue

Chest Trauma

   • two types: those found and managed in 1º survey and those found and managed in 2º survey

Table 7. Life-Threatening Chest Injuries Found in 1º Survey

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway Obstruction</td>
<td>Anxiety, stridor, hoarseness, altered mental status</td>
<td>Do not wait for ABG to intubate</td>
</tr>
<tr>
<td></td>
<td>Apena, cyanosis</td>
<td></td>
</tr>
<tr>
<td>Tension Pneumothorax</td>
<td>Respiratory distress, tachycardia, distended neck veins, cyanosis, asymmetry of chest wall motion</td>
<td>Non-radiographic diagnosis</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>Tracheal deviation away from pneumothorax</td>
<td>Percussion hyperresonance</td>
</tr>
<tr>
<td>One-way valve causing accumulation of air in pleural space</td>
<td>Unilateral absence of breath sounds</td>
<td></td>
</tr>
</tbody>
</table>
Always maintain a high index of suspicion. Do not explore penetrating neck wounds except in the OR. Management: Injuries deep to platysma require further evaluation by angiography, contrast CT, or surgery. If penetrating neck trauma present, don’t:

- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaled object

Other Potentially Life-Threatening Injuries Related to the Chest

Penetrating Neck Trauma
- Includes all penetrating trauma to the three zones of the neck
- Management: Injuries deep to platysma require further evaluation by angiography, contrast CT, or surgery
- Do not explore penetrating neck wounds except in the OR

Airway Injuries
- Always maintain a high index of suspicion

Table 7. Life-Threatening Chest Injuries Found in 1st Survey (continued)

<table>
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<tr>
<th>Condition</th>
<th>Physical Exam</th>
<th>Investigations</th>
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</tr>
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<tr>
<td>Open Pneumothorax</td>
<td>Air entering chest from wound rather than trachea</td>
<td>• Gunshot or other wound (hole &gt;2/3 tracheal diameter) ± exit wound, unequal breath sounds</td>
<td>• ABG: decreased pO2, air-tight dressing sealed on 3 sides, chest tube, surgery</td>
</tr>
<tr>
<td>Massive Hemothorax</td>
<td>&gt;1,500 cc blood loss in chest cavity</td>
<td>• Pallor, flat neck veins, shock, unilateral dullness, absent breath sounds, hypotension</td>
<td>• Usually only able to do supine CXR – entire lung appears radiopaque as blood spreads out over posterior thoracic cavity, restore blood volume, chest tube, thoracotomy if: &gt;1,500 cc total blood loss, ≥200 cc/h continued drainage</td>
</tr>
<tr>
<td>Flail Chest</td>
<td>Free-floating segment of chest wall due to &gt;2 rib fractures, each at 2 sites</td>
<td>• Paradoxical movement of flail segment, palpable crepitus of ribs, decreased air entry on affected side</td>
<td>• ABG: decreased pO2, increased pCO2, CXR: rib fractures, lung contusion, O2 + fluid therapy + pain control, judicious fluid therapy in absence of systemic hypotension, positive pressure ventilation ± intubation and ventilation</td>
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Cardiac Tamponade
- Clinical diagnosis
- Pericardial fluid accumulation impairing venous return

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<tr>
<td>Ruptured Diaphragm</td>
<td>Blunt trauma to chest or abdomen (e.g. high lap belt in MVC)</td>
<td>• Blunt trauma to chest or abdomen, CT scan and endoscopy: sometimes helpful for diagnosis</td>
<td>• Laparotomy for diaphragm repair and associated intra-abdominal injuries</td>
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<tr>
<td>Esophageal Injury</td>
<td>Usually penetrating trauma (pain out of proportion to degree of injury)</td>
<td>• CXR: mediastinal air (not always), esophagram (Gastrografin®), flexible esophagoscopy</td>
<td>• Early repair (within 24 h) improves outcome but all require repair</td>
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Aortic Tear
- 90% tear at subclavian (near ligamentum arteriosum), most die at scene
- Salvageable if diagnosis made rapidly

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<td>Blunt trauma to chest or interstitial edema impairs compliance and gas exchange</td>
<td>• CXR: areas of opacification of lung within 6 h of trauma</td>
<td>• Maintain adequate ventilation, monitor with ABG, pulse oximeter, and ECG, chest physiotherapy, positive pressure ventilation</td>
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Blunt Myocardial Injury
- Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose)
- Physical exam: overlying injury, e.g. fractures, chest wall contusion

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<td>• ECG: dysrhythmias, ST changes, patients with a normal ECG and normal hemodynamics never get dysrhythmias</td>
<td>• O2, antidysrhythmic agents, analgesia</td>
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Table 8. Potentially Life-Threatening Chest Injuries Found in 2nd Survey

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If Penetrating Neck Trauma Present, DON’T:
- Clamp structures (can damage nerves)
- Probe
- Insert NG tube (leads to bleeding)
- Remove weapon/impaled object

Other Potentially Life-Threatening Injuries Related to the Chest
• larynx
  ▪ history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma
  ▪ triad: hoarseness, subcutaneous emphysema, palpable fracture, crepitus
  ▪ other symptoms: hemoptysis, dyspnea, dysphonia
  ▪ investigations: CXR, CT scan, arteriography (if penetrating)
  ▪ management
    • airway: manage early because of edema
    • C-spine may also be injured, consider mechanism of injury
    • surgical: tracheotomy vs. repair

• trachea/bronchus
  ▪ frequently missed
  ▪ history: deceleration, penetration, increased intra-thoracic pressure, complaints of dyspnea, hemoptysis
  ▪ examination: subcutaneous air, Hamman’s sign (crunching sound synchronous with heart beat)
  ▪ CXR: mediastinal air, persistent pneumothorax or persistent air leak after chest tube inserted for pneumothorax
  ▪ management: surgical repair if >1/3 circumference

Abdominal Trauma

• two mechanisms
  ▪ blunt: usually causes solid organ injury (spleen = most common, liver = 2nd)
  ▪ penetrating: usually causes hollow organ injury or liver injury (most common)

BLUNT TRAUMA
• results in two types of hemorrhage: intra-abdominal and retroperitoneal
• adopt high clinical suspicion of bleeding in multi-system trauma

History
• mechanism of injury, SAMPLE history

Physical Exam
• often unreliable in multi-system trauma, wide spectrum of presentations
  ▪ slow blood loss not immediately apparent
  ▪ other injuries may mask symptoms
  ▪ serial examinations are required
• abdomen
  ▪ inspect: contusions, abrasions, seatbelt sign, distention
  ▪ auscultate: bruits, bowel sounds
  ▪ palpate: tenderness, rebound tenderness, rigidity, guarding
  ▪ DRE: rectal tone, blood, bone fragments, prostate location
  ▪ placement of NG, Foley catheter should be considered part of the abdominal exam
• other systems to assess: cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

Investigations
• labs: CBC, electrolytes, coagulation, cross and type, glucose, Cr, CK, lipase, amylase, liver enzymes, ABG, blood EtOH, β-hCG, U/A, toxicology screen

Table 9. Imaging in Abdominal Trauma

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td>Chest (looking for free air under diaphragm, diaphragmatic hernia, air-fluid levels), pelvis, cervical, thoracic, lumbar spines</td>
<td>Soft tissue not well visualized</td>
</tr>
</tbody>
</table>
| CT Scan                 | Most specific test                                                        | Radiation exposure 20x more than x-ray
                                                | Cannot use if hemodynamic instability            |
| Diagnostic Peritoneal   | Most sensitive test Tests for intra-peritoneal bleed                       | Cannot test for retroperitoneal bleed or diaphragmatic rupture
                                                | Cannot distinguish lethal from trivial bleed    |
| Lavage (rarely used)    |                                                                           | Results can take up to 1 h                       |
| U/S: FAST               | Identifies presence/absence of free fluid in peritoneal cavity RAPID exam: less than 5 min Can also examine pericardium and pleural cavities | NOT used to identify specific organ injuries
                                                | If patient has ascites, FAST will be falsely positive |

Seatbelt Injuries may Cause:
• Retropertioneal duodenal trauma
• Intraperitoneal bowel transection
• Meenteric injury
• L-spine injury

Indications for Foley and NG Tube in Abdominal Trauma
Foley catheter: unconscious or patient with multiple injuries who cannot void spontaneously
NG tube: used to decompress the stomach and proximal small bowel

Criteria for Positive Lavage
• >10 cc gross blood
• Bile, bacteria, foreign material
• RBC count >100,000 x 10^6/L
• WBC > 500 x 10^6/L
• Amylase >175 IU
• imaging must be done if
  ▪ equivocal abdominal examination, altered sensorium, or distracting injuries (e.g. head trauma, spinal cord injury resulting in abdominal anesthesia)
  ▪ unexplained shock/hypotension
  ▪ multiple trauma patients who must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
  ▪ fractures of lower ribs, pelvis, spine
  ▪ positive FAST

Management
• general: ABCs, fluid resuscitation, and stabilization
• surgical: watchful waiting vs. laparotomy
• solid organ injuries: decision based on hemodynamic stability, not the specific injuries
• hemodynamically unstable or persistently high transfusion requirements: laparotomy
• hollow organ injuries: laparotomy
• even if low suspicion of injury: admit and observe for 24 h

PENETRATING TRAUMA
• high risk of gastrointestinal perforation and sepsis
• history: size of blade, caliber/distance from gun, route of entry
• local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  ▪ thoracoabdominal region (may cause pneumothorax)
  ▪ back or flanks (muscles too thick)

Management
• general: ABCs, fluid resuscitation, and stabilization
• gunshot wounds → always require laparotomy

Genitourinary Tract Injuries
• see Urology, U31

Etiology
• blunt trauma: often associated with pelvic fractures
  ▪ upper tract
    ▪ renal
      ▪ contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
      ▪ parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
    ▪ ureter: rare, at uretero-pelvic junction
  ▪ lower tract
    ▪ bladder
      ▪ extraperitoneal rupture of bladder from pelvic fracture fragments
      ▪ intraperitoneal rupture of bladder from trauma and full bladder
    ▪ urethra
      ▪ posterior urethral injuries: MVCs, falls, pelvic fractures
      ▪ anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
  ▪ external genitalia
• penetrating trauma
  ▪ damage to: kidney, bladder, ureter (rare), external genitalia
• acceleration/deceleration injury
  ▪ renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
• iatrogenic
  ▪ ureter and urethra (from instrumentation)

History
• mechanism of injury
• hematuria (microscopic or gross), blood on underwear
• dysuria, urinary retention
• history of hypotension
Physical Exam
- abdominal pain, flank pain, CVA tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
- extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
- intraperitoneal bladder rupture: acute abdomen
- urethral injury: perineal ecchymosis, scrotal hematoma, blood at penile meatus, high riding prostate, pelvic fractures

Investigations
- urethra: retrograde urethrography
- bladder: U/A, CT scan, urethrogram ± retrograde cystoscopy, ± cystogram (distended bladder + post-void)
- ureter: retrograde ureterogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram

Management
- urology consult
- renal
  - minor injuries: conservative management
    - bedrest, hydration, analgesia, antibiotics
  - major injuries: admit
    - conservative management with frequent reassessments, serial U/A ± re-imaging
    - surgical repair (exploration, nephrectomy): hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis
- ureter
- ureterourethostomy
- bladder
  - extraperitoneal
    - minor rupture: Foley drainage x 10-14 d
    - major rupture: surgical repair
  - intraperitoneal
    - drain abdomen and surgical repair
- urethra
  - anterior: conservative, if cannot void → Foley or suprapubic cystostomy and antibiotics
  - posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair

Orthopedic Injuries
- see Orthopedics (Shoulder OR11, Knee OR30, Wrist OR20, Ankle OR36)

Goals of ED Treatment
- diagnose potentially life/limb threatening injuries
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

History
- use SAMPLE
- mechanism of injury may be very important

Physical Exam
- look (inspection): “SEADS” Swelling, Erythema, Atrophy, Deformity, Skin changes (e.g. bruises)
- feel (palpation): all joints/bones for local tenderness, swelling, warmth, crepitus, joint effusions, subtle deformity
- move: joints affected plus those above and below injury – active ROM preferred to passive
- neurovascular status: distal to injury (before and after reduction)
LIFE- AND LIMB-THREATENING INJURIES

Table 10. Life- and Limb-Threatening Orthopedic Injuries

<table>
<thead>
<tr>
<th>Life-Threatening Injuries (usually blood loss)</th>
<th>Limb-Threatening Injuries (usually interruption of blood supply)</th>
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<tbody>
<tr>
<td>Major pelvic fractures</td>
<td>Fracture/dislocation of ankle (talar AVN)</td>
</tr>
<tr>
<td>Traumatic amputations</td>
<td>Crush injuries</td>
</tr>
<tr>
<td>Massive long bone injuries (beeware of fat emboli)</td>
<td>Compartment syndrome</td>
</tr>
<tr>
<td>Vascular injury proximal to knee/elbow</td>
<td>Open fractures</td>
</tr>
<tr>
<td></td>
<td>Dislocations of knee/hip</td>
</tr>
<tr>
<td></td>
<td>Fractures above knee/elbow</td>
</tr>
</tbody>
</table>

Open Fractures
- communication between fracture site and external surface of skin – increased risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- must secure definitive surgical care within 6-8 h

Vascular Injuries
- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

Compartment Syndrome
- increased interstitial pressure in an anatomical “compartment” (forearm, calf) with little room for expansion, resulting in decreased perfusion and potential muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - look for “the 6 Ps”
- requires prompt decompression: remove constrictive casts, dressings; fasciotomy may be needed emergently

UPPER EXTREMITY INJURIES
- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
    - reduce (traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with orthopedics
    - with forceful injury, look for fracture
- Colles’ fracture
  - distal radius fracture with dorsal displacement from “Fall on Outstretched Hand” (FOOSH)
  - AP film: shortening, radial deviation, radial displacement
  - lateral film: dorsal displacement, volar angulation
  - reduce, immobilize with splint, out-patient follow-up with orthopedics or immediate orthopedics referral if complicated fracture
  - if involvement of articular surface, emergent orthopedic referral
  - scaphoid fracture
    - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
    - negative x-ray: thumb spica splint, repeat x-ray in 1 wk ± bone scan
    - positive x-ray: thumb spica splint x 6-8 wk, repeat x-ray in 2 wk
    - risk of AVN of scaphoid if not immobilized
    - outpatient orthopedic follow-up

LOWER EXTREMITY INJURIES
- ankle and foot fractures
  - see Ottawa Ankle and Foot Rules
- knee injuries
  - see Ottawa Knee Rules
• avulsion of the base of 5th metatarsal
  ▪ occurs with inversion injury
  ▪ supportive tensor or below knee walking cast for 3 wk

• calcaneal fracture
  ▪ associated with fall from height
  ▪ associated injuries may involve ankles, knees, hips, pelvis, lumbar spin

A knee x-ray examination is required only for acute injury patients with one or more of:

• Age 55 yr or older
• Tenderness at head of fibula
• Isolated tenderness of patella
• Inability to flex to 90º
• Inability to bear weight both immediately and in ED (four steps)

Wound Management

Goals of ED Treatment

• identify injuries and stop any active bleeding – direct pressure
• manage pain
• wound examination and exploration (history and physical)
• cleansing ± antibiotic and tetanus prophylaxis
• closure and dressing

Tetanus Prophylaxis

• both tetanus toxoid (Td) and immunoglobulin (TIG) are safe in pregnancy

Table 11. Guidelines for Tetanus Prophylaxis for Wounds

<table>
<thead>
<tr>
<th>Immunization History</th>
<th>Non-Tetanus Prone Wounds</th>
<th>Tetanus Prone Wounds¹</th>
<th>Approx. Duration (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Td¹</td>
<td>TIG²</td>
<td>Td</td>
</tr>
<tr>
<td>Uncertain or &lt;3 doses</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3 or more, none for &gt;10 yr</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3 or more, 5 to 10 yr ago</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3 or more, &lt;4 yr ago</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

¹ wounds >6 h old, >1 cm deep, puncture wounds, avulsions, wounds resulting from missiles, crush wounds, burns, frostbite, wounds contaminated with dirt, feces, soil, or saliva

² 0.5 mL IM tetanus and diphtheria toxoids (Td), adsorbed
³ tetanus immune globulin (TIG), 250 units deep IM


Accuracy of Ottawa Ankle Rules to Exclude Fractures of the Ankle and Mid-Foot: Systematic Review

This systematic review and meta-analysis of 27 studies including 15,561 patients evaluated the sensitivity and specificity of the Ottawa Ankle Rules for excluding fractures of the ankle and mid-foot.

Results: The pooled likelihood ratio of a negative result (obtaining a false negative) among those with a fracture was determined to be 0.08 for both the ankle and mid-foot.

Conclusions: The Ottawa Ankle Rules provide an accurate instrument for excluding fractures of the ankle and mid-foot with a sensitivity of almost 100% and a specificity of 26%. The use of this instrument can reduce the number of unnecessary radiographs.
Brises
• non-palpable = ecchymosis
• palpable collection (not swelling) = hematoma following blunt trauma
• assess for coagulopathy (e.g. liver disease), anticoagulant use

Abrasions
• partial to full thickness break in skin
• management
  ▪ clean thoroughly with brush to prevent foreign body impregnation ± local anesthetic
  ▪ antiseptic ointment (Polysporin® or Vaseline®) for 7 d for facial and complex abrasions
  ▪ tetanus prophylaxis

Lacerations
• see Plastic Surgery, PL8
• consider every structure deep to a laceration injured until proven otherwise
• in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury
• physical exam
  ▪ think about underlying anatomy
  ▪ examine tendon function actively against resistance and neurovascular status distally
  ▪ clean and explore under local anesthetic; look for partial tendon injuries
• management
  ▪ disinfect skin/use sterile techniques
  ▪ irrigate copiously with NS
  ▪ analgesia ± anesthesia
  ▪ maximum dose of lidocaine:
    ▪ 7 mg/kg with epinephrine
    ▪ 5 mg/kg without epinephrine
• in children, topical anesthetics such as LET (lidocaine, epinephrine and tetracaine), and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
• secure hemostasis
• evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
• ± prophylactic antibiotics (consider for animal/human bites, intraoral lesion, or puncture wounds to the foot)
• suture unless: delayed presentation (>6-8 h), puncture wound, mammalian bite, crush injury, or retained foreign body
  ▪ take into account patient and wound factors when considering suturing
• advise patient when to have sutures removed
• cellulitis and necrotising fasciitis, see Plastic Surgery, PL14

Approach to Common ED Presentations

Abdominal Pain

Rule Out Life-Threatening Causes
• CVS: MI, aortic dissection (tearing pain), ruptured AAA
• GI: perforated viscus, hepatic/splenic injury, ischemic bowel (diffuse pain), strangulated hernia
• gynecologic: ectopic pregnancy

Additional Differential Diagnosis
• GI: appendicitis, diverticulitis, bowel obstruction, hepatitis, cholecystitis, pancreatitis
• urinary: pyelonephritis, ureteral calculi, cystitis
• genital
  ▪ female: tubo-ovarian abscess, ovarian torsion, ovarian cyst, salpingitis, PID, endometriosis
  ▪ male: testicular torsion, epididymitis, prostatitis
• other: DKA, herpes zoster virus, intra-abdominal abscess, pneumonia, lead poisoning, porphyria, sickle cell crisis, acute angle closure glaucoma, Addison’s crisis, psychiatric

History
• pain: OPQRST
• broad differential, including GU, gynecological, GI, respiratory, and CV systems
• recent/remote abdominal trauma/surgeries
• most recent colonoscopy

Alternatives to Sutures
• tissue glue
• Steristrips®
• staples

Where NOT to use local anesthetic with epinephrine:
• ears, nose, fingers, toes, and penis

High Risk Factors for Infection

Wound Factors
• puncture wounds
• crush injuries
• wounds >12 h old
• hand or foot wounds
• immunocompromised

Patient Factors
• age >50 yr
• prosthetic joints or valves (risk of endocarditis)

Early wound irrigation and debridement are the most important factors in decreasing infection risk

Be vigilant in those at extremes of ages (very young, elderly) as they often present atypically

Old age, pregnancy (T3), and chronic corticosteroid use can blunt peritoneal findings, so have an increased suspicion of intra-abdominal process in these individuals

If elevated AST and ALT:
think hepatocellular injury
AST > ALT: alcohol-related
ALT > AST: viral, drug, toxin
If elevated ALP and GGT:
think biliary tree stones
Physical Exam
- vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and CVS as indicated by history

Investigations
- do not delay consultation if patient unstable
- CBC, electrolytes, glucose, BUN/Cr, U/A ± LFTs, lipase, β-hCG, ECG, troponins
- AXR: look for calcifications, free air, gas pattern, air fluid levels
- CXR upright: look for pneumoperitoneum (free air under diaphragm)
- U/S: biliary tract, ectopic pregnancy, AAA, free fluid
- CT: trauma, AAA, pancreatitis, nephro/uroolithiasis, appendicitis, and diverticulitis

Management
- NPO, IV, NG tube, analgesics, consider antibiotics and anti-emetics
- growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
- consult as necessary: general surgery, vascular surgery, gynecology, etc.

Disposition
- admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
- discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develop

Acute Pelvic Pain

Etiology
- gynecological
  - ovaries: ruptured ovarian cysts (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass)
  - fallopian tubes: salpingitis, tubal abscess, hydrosalpinx
  - uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in pregnant patient (degeneration), PID, endometriosis
  - other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), endometriosis and dysmenorrhea, sexual, or physical abuse
- non-gynecological
  - GI: appendicitis, constipation, bowel obstruction, gastroenteritis, diverticulitis, IBD, IBS
  - GU: cystitis, pyelonephritis, ureteric stone
  - other: porphyria, abdominal angina, aneurysm, hernia, zoster, psychological abuse/domestic violence

History and Physical Exam
- pain: OPQRST
- associated symptoms: vaginal bleeding, bowel or bladder symptoms, radiation
- vitals
- gynecological exam: assess for cervical motion tenderness/“chandelier sign” (suggests PID)
- abdominal exam

Investigations
- blood work
  - β-hCG for all women of childbearing age
- CBC and differential, electrolytes, glucose, BUN/Cr, G&S, PTT/INR
- imaging
  - pelvic and abdominal U/S: evaluate adnexa, look for free fluid or masses in the pelvis, evaluate thickness of endometrium, confirm intrauterine pregnancy if β-hCG positive
- doppler flow studies for ovarian torsion

Management
- general: analgesia, determine if admission and consults are needed
- specific
  - ovarian cysts
    - unruptured or ruptured and hemodynamically stable: analgesia and follow-up
    - ruptured with significant hemoperitoneum: may require surgery
  - ovarian torsion: surgical detorsion or removal of ovary
  - uncomplicated leiomyomas, endometriosis, and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  - PID: requires broad spectrum antibiotics
Disposition
• referral: gynecological or obstetrical causes requiring surgical intervention, requiring admission, or oncological in nature
• admission: patients requiring surgery, IV antibiotics/pain management
• discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

Altered Level of Consciousness

Definitions
• altered mental status: collective, non-specific term referring to change in cognitive function, behavior, or attentiveness, including:
  ▪ delirium (see Psychiatry, PS16)
  ▪ dementia (see Psychiatry, PS17)
  ▪ lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  ▪ stupor: unresponsive but arousable
  ▪ coma: a sleep-like state, not arousable to consciousness
• use the GCS to evaluate LOC (see Initial Patient Assessment/Management, ER2)

Figure 11. Etiology of coma

MANAGEMENT OF ALTERED LOC

History
• obtain collateral from family, friends, police, paramedics, old chart, etc.
• onset and progression
  ▪ abrupt onset suggests CNS hemorrhage/ischemia or cardiac cause
  ▪ progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
• preceding events
  ▪ it is essential to determine patient’s baseline LOC
  ▪ antecedent trauma, seizure activity, fever
  ▪ past medical history (e.g. similar episode, depression, overdose)

Physical Exam
• ABCs, vitals including temperature, cardiac, chest, respiratory, abdominal exam
• complete neuro exam, in particular examination of the eyes (pupil size and reactivity), look for MedicAlert* bracelet

Investigations
• blood work
  ▪ rapid blood sugar, CBC, electrolytes, Cr, BUN, LFTs, glucose, serum osmolality, VBG, PT/PTT/INR, troponins
  ▪ serum EtOH, acetaminophen, and salicylate levels
• imaging
  ▪ CXR, CT head
• other tests
  ▪ ECG, U/A, UTox
Diagnosis
- administer appropriate universal antidotes
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished
  - one ampule D50W IV if low blood sugar on finger-prick
  - naloxone 0.4-2 mg IV or IM if opiate overdose suspected
- distinguish between structural and toxic-metabolic coma
  - structural coma
    - pupils, extraocular movements, and motor findings, if present, are usually asymmetric
    - look for focal or lateralizing abnormalities
  - toxic-metabolic coma
    - dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
    - respiratory depression in association with an intact upper brainstem (e.g. equal and reactive pupils; see exceptions in Table 12)
    - extraocular movements and motor findings are symmetric or absent
- essential to re-examine frequently because status can change rapidly
- diagnosis may become apparent only with the passage of time
  - delayed deficit after head trauma suggestive of epidural hematoma (characteristic "lucid interval")

Table 12. Toxic-Metabolic Causes of Fixed Pupils

<table>
<thead>
<tr>
<th>Dilated</th>
<th>Dilated to Normal</th>
<th>Constricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anoxia</td>
<td>Hypothermia</td>
<td>Cholinergic agents (e.g. organophosphates)</td>
</tr>
<tr>
<td>Anticholinergic agents (e.g. atropine, TCAs)</td>
<td>Barbiturates</td>
<td>Opiates (e.g. heroin), except meperidine</td>
</tr>
<tr>
<td>Methanol (rare)</td>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinogens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disposition
- admission: if ongoing decreased LOC, admit to service based on tentative diagnosis, or transfer patient if appropriate level of care not available
- discharge: readily reversible alteration of LOC; ensure adequate follow-up care available

Chest Pain

Rule Out Life-Threatening Causes
- CVS: ACS, pericarditis, cardiac tamponade, aortic dissection
- respiratory: PE, pneumothorax (tension or spontaneous)
- GI: esophageal rupture, pneumomediastinum

Additional Differential Diagnosis
- cardiac: stable angina
- respiratory: pneumonia
- GI: peptic ulcer disease, pancreatitis, cholecystitis, esophagitis, reflux, esophageal spasm
- MSK: rib fractures, costochondritis, zoster, etc.
- psychogenic/anxiety (diagnosis of exclusion)

Initial Resuscitation and Management
- O2, IV, cardiac monitoring, CXR (portable if unstable), ECG

History
- must evaluate cardiac risk factors (see TIMI Score, Cardiology and Cardiac Surgery, C27)
  - classic presentations (but presentation seldom classic)
    - aortic dissection: syncope with sudden severe tearing pain, often radiating to back ± focal pain/neuroligic loss in extremities secondary to major vessel ischemia
    - PE: pleuritic chest pain (75%), dyspnea, anxiety, tachycardia, PERC Score
    - pericarditis: anterior precordial pain, pleuritic, relieved by sitting up and leaning forward
    - ACS: retrosternal squeezing/pressure pain, radiation to arm/neck, dyspnea, N/V, syncope
    - esophageal: frequent heartburn, acid reflex, dysphagia, relief with antacids
  - ACS more likely to be atypical in females, diabetics, and >80 yr

Physical Exam
- vitals (BP in both arms, but unreliable indicator of dissection)
- palpate chest wall for tender points; present in 25% of acute MI, but may suggest MSK cause if symptoms fully reproduced and all serious etiologies have been ruled out
- cardiac, respiratory, and peripheral vascular exams
Table 13. Common Life-Threatening ECG Changes

<table>
<thead>
<tr>
<th>Pathology</th>
<th>ECG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysrhythmia</strong></td>
<td></td>
</tr>
<tr>
<td>a) Torsades de pointes</td>
<td>Ventricular complexes in upward-pointing and downward-pointing continuum (250-350 bpm)</td>
</tr>
<tr>
<td>b) Ventricular tachycardia</td>
<td>6 or more consecutive premature ventricular beats (150-250 bpm)</td>
</tr>
<tr>
<td>c) Ventricular flutter</td>
<td>Smooth sine wave pattern of similar amplitude (250-350 bpm)</td>
</tr>
<tr>
<td>d) Ventricular fibrillation</td>
<td>Erratic ECG tracing, no identifiable waves</td>
</tr>
<tr>
<td><strong>Conduction</strong></td>
<td></td>
</tr>
<tr>
<td>a) 2nd degree heart block (Mobitz Type II)</td>
<td>PR interval stable, some QRSs dropped</td>
</tr>
<tr>
<td>b) 3rd degree heart block</td>
<td>Total AV dissociation, but stable P-R and R-R intervals</td>
</tr>
<tr>
<td>c) Left bundle branch block</td>
<td>Prolonged QRS complex (t &gt;0.12 s)</td>
</tr>
<tr>
<td></td>
<td>RSR' in V5 or V6</td>
</tr>
<tr>
<td></td>
<td>Monophasic I and V6</td>
</tr>
<tr>
<td></td>
<td>May see ST elevation</td>
</tr>
<tr>
<td></td>
<td>Difficult to interpret, new LBBB considered STEMI equivalent</td>
</tr>
<tr>
<td><strong>Ischemia</strong></td>
<td></td>
</tr>
<tr>
<td>a) STEMI</td>
<td>ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression)</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>a) Hyperkalemia</td>
<td>Tall T waves</td>
</tr>
<tr>
<td></td>
<td>P wave flattening</td>
</tr>
<tr>
<td>b) Hypokalemia</td>
<td>QRS complex widening and flattening</td>
</tr>
<tr>
<td></td>
<td>U waves appear</td>
</tr>
<tr>
<td></td>
<td>Flattened T waves</td>
</tr>
<tr>
<td><strong>Digitalis Toxicity</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gradual downward curve of ST.</td>
</tr>
<tr>
<td></td>
<td>At risk for AV blocks and ventricular irritability</td>
</tr>
<tr>
<td><strong>Syndromes</strong></td>
<td></td>
</tr>
<tr>
<td>a) Brugada</td>
<td>RBBB with ST elevation in V1, V2, and V3</td>
</tr>
<tr>
<td></td>
<td>Susceptible to deadly dysrhythmias, including ventricular fibrillation</td>
</tr>
<tr>
<td>b) Wellens</td>
<td>Marked T wave inversion in V2 and V3</td>
</tr>
<tr>
<td></td>
<td>Left anterior descending coronary stenosis</td>
</tr>
<tr>
<td>c) Long QT syndrome</td>
<td>QT interval longer than ½ of cardiac cycle</td>
</tr>
<tr>
<td></td>
<td>Predisposed to ventricular dysrhythmias</td>
</tr>
</tbody>
</table>
ACUTE MYOCARDIAL INFARCTION
• see Cardiology and Cardiac Surgery, C27

Management
• immediate stabilization
  ▪ oxygen 4 L/min
  ▪ IV access
  ▪ cardiac monitors
  ▪ STAT ECG
  ▪ cardiac enzymes (CK, troponins)
• ASA 162-325 mg chewed
• nitroglycerin 0.3 mg SL q5min x 3 (IV for CHF, HTN, unresolved pain)
  ▪ do not use if patient is hypotensive or in the setting of an inferior MI
• morphine 2-5 mg IV q5-30min if unresponsive to nitroglycerin
  ▪ do not use if patient is hypotensive or in the setting of an inferior MI
• low molecular weight heparin 1 mg/kg SC bid (30 mg IV STAT post TNK/tenecteplase infusion)
• thrombolytics (within 30 min) or primary percutaneous coronary intervention (within 90 min)
  ▪ agents include rt-PA, streptokinase, and TNK
  ▪ evaluate indications and contraindications prior to use
• other: antidysrhythmics, cardioversion, defibrillation, transthoracic pacing, angioplasty
• cardiology consult

Epistaxis
• see Otolaryngology, OT27
• 90% of nosebleeds stem from the anterior nasal septum (at Kieselbach’s plexus located in Little’s area)
• can be life-threatening

Etiology
• most commonly caused by trauma (digital, blunt, foreign bodies)
• other causes: barometric changes, nasal dryness, chemicals (cocaine, Otrivin†), or systemic disease (coagulopathies, HTN, etc.)

Investigations
• blood work: CBC, PT/PTT (as indicated)
• imaging: x-ray, CT as needed

Treatment
• aim is to localize bleeding and achieve hemostasis
• first-aid: ABCs, clear clots by blowing nose or suctioning, lean forward, pinch cartilaginous portion of nose for 20 min twice
• assess blood loss: vitals, IV NS, cross match 2 units pRBC if significant
• if first aid measures fail twice, proceed to packing
• apply an anterior pack
  ▪ clear nose of any clots
  ▪ apply topical anesthesia/vasoconstrictors (lidocaine with epinephrine, cocaine, or soaked pledgets)
  ▪ insert either a traditional Vaseline† gauze pack or a commercial nasal tampon or balloon
  ▪ if bleeding stops, arrange follow-up in 48-72 h for reassessment and pack removal
  ▪ prophylactic anti-staphylococcal antibiotics should be prescribed to prevent sinusitis or toxic shock syndrome
  ▪ if bleeding is controlled with anterior pressure, cautery with silver nitrate can be performed
    ▪ if the site of bleeding is identified (one side of septum only because if both are cauterized this can lead to septal perforation)
  ▪ if suspect posterior bleed or anterior packing does not provide hemostasis, consult ENT for posterior packing and further evaluation
• posterior packing (ENT consult)
  ▪ posterior packing requires monitoring because can cause significant vagal response and posterior bleeding source can lead to significant blood loss

Disposition
• discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. humidifiers, saline spray, topical ointments, avoiding irritants, managing HTN)
• admission: severe cases of refractory bleeding
Headache

- see Neurology, N43

Etiology

- the common
  - common migraine (no aura)/classic migraine (with aura)
    - gradual onset, unilateral/bilateral, throbbing
    - N/V, photo/phonophobia
    - treatment: analgesics, antiepileptic drugs, vasoactive medications
  - tension/muscular headache
    - never during sleep, gradual over 24 h
    - posterior/occipital
    - increased with stressors
    - treatment: modify stressor(s), local measures, NSAIDs, tricyclic antidepressants

- the deadly
  - SAH (see Neurosurgery, NS18)
    - sudden onset, increased with exertion
    - reaches maximum intensity within minutes, N/V, meningeal signs
    - diagnosis: CT, LP (5-10% of patients with SAH have negative initial CT)
      - sensitivity of CT decreases with time and is much less sensitive by 48-72 h
    - management: urgent neurosurgery consult
  - increased ICP
    - worse in morning, when supine or bending down, with cough or Valsalva
    - physical exam: neurological deficits, cranial nerve palsies, papilledema
    - diagnosis: CT scan
    - management: consult neurosurgery
  - meningitis (see Infectious Diseases, ID19)
    - flu-like presentation initially (fever, N/V, malaise), meningeal signs, purpuric rash
    - altered LOC and confusion
    - perform CT to rule out increased ICP then do LP for diagnosis
    - treatment: early empiric antibiotics (depending on age group), steroid therapy
  - temporal arteritis (causes significant morbidity, blindness) (see Ophthalmology, OP38)
    - unilateral scalp tenderness, jaw claudication, visual disturbances
    - labs: elevated ESR, CRP
    - temporal artery biopsy is gold standard for diagnosis
    - associated with polymyalgia rheumatica
    - treatment: high-dose steroids immediately if suspected

Disposition

- admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications
- discharge: assess for risk of narcotic misuse, most patients can be discharged with appropriate analgesia and follow-up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

Joint Pain

- see Rheumatology, RH3

Rule Out Life-Threatening Causes

- septic joint (see Orthopedics, OR10)

Differential Diagnosis

- articular pain
  - monoarticular
    - infectious: bacterial, viral, fungal
    - hemarthrosis: trauma/fracture, anticoagulants, bleeding diatheses
    - crystal induced: gout, calcium pyrophosphate deposition, hydroxyapatite
    - inflammatory: seropositive, seronegative
    - neoplasm
    - degenerative: osteoarthritis
  - polyarticular
    - infectious: Lyme disease, bacterial endocarditis, septicemia, gonococcus, viral
    - post-infectious: rheumatic fever, reactive arthritis, enteric infections
    - inflammatory: seropositive, seronegative
    - degenerative: osteoarthritis

Dexamethasone for Reduction of Migraine Recurrence

Shows that a single dose of IV dexamethasone may decrease recurrence of migraine within 24 h [NNT 10].

Note: up to 5% of patients with SAH have a normal CT scan; if suspect SAH with a negative CT, perform a LP

DDx Subarachnoid Hemorrhage

BATS
Berry aneurysm
Arteriovenous malformation
Adult polycystic kidney disease
Trauma
Stroke

Meningitis

- Do not delay IV antibiotics for LP
- Deliver 1st dose of dexamethasone with or before 1st doses of antibiotic therapy

Ottawa SAH Rules

- For alert patients older than 15 yr with new severe non-traumatic headache reaching maximum intensity within 1 h
- Not for patients with new neurologic deficits, previous aneurysms, SAH, brain tumors, or history of recurrent headaches (≥3 episodes over the course of ≥6 mo)
- Investigate if ≥1 high-risk variables present:
  - Age ≥40 yr
  - Neck pain or stiffness
  - Witnessed loss of consciousness
  - Onset during exertion
  - Thunderclap headache (instantly peaking pain)
  - Limited neck flexion on examination
• non-articular
  ▪ localized: tendinitis, bursitis, capsulitis, muscle sprain
  ▪ generalized: fibromyalgia, polymyalgia rheumatica
• other
  ▪ neurologic: spinal stenosis/spondylolisthesis, degenerative disc disease, cauda equina syndrome, neoplasm, thoracic outlet syndrome, Charcot joint
  ▪ vascular: intermittent claudication

History and Physical Exam
• associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis
• patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric
• inflammatory symptoms: prolonged morning stiffness, stiffness and pain ease through the day, midday fatigue, soft tissue swelling
• non-inflammatory symptoms: stiffness short lived after inactivity, short duration stiffness in the morning, pain increases with activity
• assess ROM, presence of joint effusion, warmth
• assess for localized joint pain, erythema, warmth, swelling with pain on active ROM, inability to bear weight, fever; may indicate presence of septic joint

Investigations
• blood work
  ▪ CBC, ESR, CRP, WBC, INR/PTT, blood cultures, urate
• imaging
  ▪ joint x-ray ± contralateral joint for comparison
• other investigations
  ▪ joint aspirate → send for: WBC, protein, glucose, Gram stain, crystals

Management
• septic joint: IV antibiotics ± joint decompression and drainage
  ▪ antibiotics can be started empirically if septic arthritis cannot be ruled out
• crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids
  ▪ do not use allopurinol, as it may worsen acute attack
• acute polyarthritis: NSAIDs, analgesics (acetaminophen ± opioids), local or systemic corticosteroids
• osteoarthritis: NSAIDs, acetaminophen
• soft tissue pain: allow healing with enforced rest ± immobilization
  ▪ non-pharmacologic treatment: local heat or cold, electrical stimulation, massage
  ▪ pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

Hospitalization is required for joint pain in the presence of:
• Significant, concomitant internal organ involvement
• Signs of bacteremia, including vesiculopustular skin lesions, Roth spots, shaking chills, or splinter hemorrhages
• Systemic vasculitis
• Severe pain
• Severe constitutional symptoms
• Purulent synovial fluid in one or more joints
• Immunosuppression

Otalgia

Differential Diagnosis (see Otolaryngology, OT6)
• local
  ▪ infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis in diabetics, herpes simplex/zoster, auricular cellulitis, external canal abscess, dental disease
  ▪ others: trauma, temporomandibular joint dysfunction, neoplasm, foreign body, cerumen impactions, trigeminal neuralgia, granulomatosis with polyangiitis

History
• OPQRST
• associated symptoms: aural fullness (feeling of pressure), otorrhea, hearing loss, tinnitus, vertigo, pruritis, fever
• risk factors: Q-tip use, hearing aids, headphones

Physical Exam
• observe for otorrhea, palpation of outer ear/mastoid, otoscope to see bulging erythematous tympanic membrane, perforation

Investigations
• consider audiogram if hearing loss
• C&S of ear canal discharge, if present
• CT head if suspicion of mastoiditis, malignant otitis media

Management
• debridement of cerumen or exudates
• antibiotics/antifungals/antivirals for respective infections
Seizures

• see Neurology, N16

Definition
• paroxysmal alteration of behavior and/or EEG changes resulting from abnormal, excessive activity of neurons
• status epilepticus: continuous or intermittent seizure activity for greater than 5 min without regaining consciousness

Categories
• generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
• partial seizure (local): simple partial, complex partial
• causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP), metabolic disturbance (hypo/hyperglycemia, hypo/hypernatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
• differential diagnosis: syncope, pseudoseizures, migraines, movement disorders, narcolepsy/cataplexy, myoclonus

History
• from patient and bystander: flaccid and unconscious, often with deep rapid breathing
• preceding aura, rapid onset, loss of bladder/bowel control, tongue-biting (sides of the tongue)
• timing: length of seizure

Physical Exam
• injuries to head and spine and bony prominences (e.g. elbows), tongue laceration, aspiration, urinary incontinence

Investigations
• known seizure disorder: antiepileptic drug levels
• Accu-Chek®
• first time seizure: CBC, serum glucose, electrolytes, BUN/Cr, Ca²⁺, Mg²⁺; consider prolactin, β-hCG, toxicology screen
• initial imaging: CT; x-ray if suspected extremity injuries; definitive imaging: MRI, EEG

Table 14. Management of Status Epilepticus

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>Give oxygen; ensure adequate ventilation Monitor: vital signs, ECG, axiometry Establish IV access; obtain blood samples for glucose level, CBC, electrolytes, toxins, and antiepileptic drug levels</td>
</tr>
<tr>
<td>6-9</td>
<td>Give 50 mL 50% glucose (preceded by thiamine 100 mg IM in adults)</td>
</tr>
<tr>
<td>10-20</td>
<td>IV lorazepam 0.1 mg/kg at 2 mg/min or IV diazepam 0.2 mg/kg at 5 mg/min Diazepam can be repeated if seizures do not stop after 5 min; if diazepam is used to stop the status, then phenytoin should be administered promptly to prevent the recurrence of status</td>
</tr>
<tr>
<td>21-60</td>
<td>If status persists, administer 15-20 mg/kg of phenytoin intravenously no faster than 50 mg/min in adults and 1 mg/kg/min in children</td>
</tr>
<tr>
<td>&gt;60</td>
<td>If status does not stop after 20 mg/kg of phenytoin, give additional doses of 5 mg/kg to a maximal dose of 30 mg/kg If status persists, then give 20 mg/kg of phenobarbital IV at 100 mg/min; when phenobarbital is given after a benzodiazepine, ventilatory assistance is usually required If status persists, then give general anesthesia (e.g. pentobarbital); vasopressors or fluid volume are usually necessary, EEG should be monitored; neuromuscular blockade may be needed</td>
</tr>
</tbody>
</table>

Adapted from: Cecil Essentials of Medicine, 7th edition, Table 125-7. Used with permission

Disposition
• the decision to admit or discharge should be based on the underlying disease process identified
  ▶ if a patient has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
• first-time seizure patients being discharged should be referred to a neurologist for follow-up
• admitted patients should generally have a neurology consult
• patient should not drive until medically cleared (local regulations vary)
  ▶ complete notification form to appropriate authority regarding ability to drive
• warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)
Shortness of Breath

- see Respirology, R3 and Cardiology and Cardiac Surgery, C5

Etiology
- categorized into one of two groups: respiratory or cardiovascular
- respiratory system dyspnea: disorders of the central controller (brain), the ventilatory pump (ventilatory muscles, peripheral nerves), and the gas exchanger (alveoli and pulmonary capillaries)
- cardiovascular system dyspnea: cardiac diseases (acute ischemia, heart failure, systolic dysfunction, valvular disorders, pericardial diseases, arrhythmias), anemia, and deconditioning

History and Physical Exam
- acute SOB is often due to a relatively limited number of conditions; associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischemia
  - fever, cough, and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
  - chest tightness may be indicative of bronchospasm
  - a sensation of rapid, shallow breathing may correspond to interstitial disease
  - a sense of heavy breathing is typical of deconditioning
  - ask about environmental or occupational exposures
- dyspnea may be the sole complaint and the physical exam may reveal few abnormalities (e.g. PE, pneumothorax)
- vitals including pulse oximetry
  - wheeze (airway) vs. crackles (parenchymal), JVP, and murmurs

Investigations
- blood work
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider VBG
  - serial cardiac enzymes and ECG if considering cardiac source
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection, or interstitial fluid)
  - CT chest usually is not indicated in the initial evaluation of patients with dyspnea, but can be valuable in patients with interstitial lung disease, occult emphysema, or chronic thromboembolic disease (i.e. PE)

Management of Life-Threatening Dyspnea NYD
- see Primary and Secondary Surveys, ER2, ER5
- treat underlying cause

Disposition
- the history and physical exam lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified
  - consider intubation in CO2 retainers (e.g. COPD)
- if the decision to discharge is chosen, provide appropriate discharge instructions to return in case of returning/worsening SOB

Syncope

Definition
- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system hypoperfusion

Etiology
- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, tamponade, tension pneumothorax, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)

History
- gather details from witnesses, and clarify patient’s experience (e.g. dizziness, ataxia, or true syncope)
  - two key historical features: prodrome and situation
distinguish between syncope and seizure (see Neurology, N16)
  - some patients may have myoclonic jerks with syncope - NOT a seizure
  - signs and symptoms during presyncope, syncope, and postsyncope
  - past medical history, drugs
  - think anatomically in differential; pump (heart), blood, vessels, brain
  - syncope is cardiogenic until proven otherwise if:
    - there is sudden loss of consciousness with no warning or prodrome
    - syncope is accompanied by chest pain

Physical Exam
- postural BP and HR
- cardiovascular, respiratory, and neurological exam
- physical findings in the elderly patient who falls (I HATE FALLING):
  - Inflammation of joints (or joint deformity)
  - Hypotension (orthostatic BP changes)
  - Auditory and visual abnormalities
  - Tremor (Parkinson’s disease or other causes of tremor)
  - Equilibrium (balance) problem
  - Foot problems
  - Arrhythmia (dysrhythmia), heart block, or valvular disease
  - Leg-length discrepancy
  - Lack of conditioning (generalized weakness)
  - Illness
  - Nutrition (poor; weight loss)
  - Gait disturbance

Investigations
- ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval), bedside glucose
- blood work: CBC, electrolytes, BUN/Cr, ABGs, troponin, Ca²⁺, Mg²⁺, β-hCG
- consider toxicology screen

Management
- ABCs, IV, O₂, monitor
- examine for signs of trauma caused by syncopal episode
- cardiogenic syncope: admit to medicine/cardiology
- low risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

Disposition
- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow up with family physician
  - educate regarding avoiding orthostatic or situational syncope
  - evaluate the patient for fitness to drive or work
  - patients with recurrent syncope should avoid high-risk activities (e.g. driving)

Sexual Assault

Epidemiology
- 1 in 4 women and 1 in 10 men will be sexually assaulted in their lifetime
- it is estimated that only 7% of rapes are reported

General Approach
- ABCs, treat acute, serious injuries
- ensure patient is not left alone and provide ongoing emotional support
- set aside adequate time for exam (usually 1.5 h)
- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained)
- Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests (legally required if <16 yr old)

History
- ensure privacy for the patient – others should be asked to leave
- questions to ask: who, when, where did penetration occur, what happened, any weapons or physical assault?
- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
  - gravidity, parity, last menstrual period
  - contraception use
  - last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.

**Physical Exam**
- evidence collection is always secondary to treatment of serious injuries
- never re-traumatize a patient with the examination
- general examination
  - mental status
  - sexual maturity
  - patient should remove clothes and place in paper bag
  - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
- pelvic exam and specimen collection
  - ideally before urination or defecation
  - examine for seminal stains, hymen, signs of trauma
  - collect moistened swabs of dried seminal stains
  - pubic hair combings and cuttings
  - speculum exam
    - lubricate with water only
    - vaginal lacerations, foreign bodies
    - Pap smear
    - oral/cervical/rectal culture for gonorrhea and chlamydia
    - posterior fornix secretions if present or aspiration of saline irrigation
    - immediate wet smear for motile sperm
    - air-dried slides for immotile sperm, acid phosphatase, ABO group
- others
  - fingernail scrapings
  - saliva sample from victim

**Investigations**
- VDRL: repeat in 3 mo if negative
- serum β-hCG
- blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

**Management**
- involve local/regional sexual assault team
- medical
  - suture lacerations
  - tetanus prophylaxis
  - gynecology consult for foreign body, complex lacerations
  - assumed positive for gonorrhea and chlamydia
    - management: azithromycin 1 g PO x 1 dose (alt: doxycycline 100 mg PO bid x 7 d) and cefixime 800 mg PO x 1 dose (alt: ceftriaxone 1 g IM x 1 dose)
  - may start prophylaxis for hepatitis B and HIV
  - pre and post counseling for HIV testing
  - pregnancy prophylaxis offered
    - levonorgestrel 0.75 mg PO STAT, repeat within 12 h (Plan B)
- psychological
  - high incidence of psychological sequelae
  - have victim change and shower after exam completed

**Disposition**
- discharge if injuries/social situation permit
- follow-up with physician in rape crisis center within 24 h
- best if patient does not leave ED alone

**DOMESTIC VIOLENCE**
- women are usually the victims, but male victimization also occurs
- identify the problem (need high index of suspicion)
  - suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns, or other injuries; often inconsistent with history provided)
  - somatic symptoms (chronic and vague complaints)
  - psychosocial symptoms
  - clinician impression (your ‘gut feeling’, e.g. overbearing partner that won't leave patient's side)
- if disclosed, be supportive and assess danger
- patient must consent to follow-up investigation/reporting (unless for children)
Management

- treat injuries
- ask about sexual assault and children at home (encourage notification of police)
- document findings
- safety plan
- follow-up: family doctor/social worker

Medical Emergencies

Anaphylaxis and Allergic Reactions

Etiology

- anaphylaxis is an exaggerated immune mediated hypersensitivity reaction that leads to systemic histamine release, increased vascular permeability, and vasodilation; regardless of the etiology, the presentation and management of anaphylactic reactions are the same
  - allergic (re-exposure to allergen)
  - non-allergic (e.g. exercise induced)

Presentation

- classic presentation of anaphylaxis includes
  1. rapid onset and progression of symptoms
  2. life-threatening compromise of one or more of airway (breathing/swallowing difficulty, stridor, voice change), breathing (SOB, hypoxemia, wheezing, respiratory arrest), and circulation (tachycardia, hypotension, confusion, decreased urine output, chest pain)
  3. involvement of skin (erythema, urticaria, warmth) and/or mucosa (angioedema, obstruction, GI symptoms) not always present

Management

1. immediate initial management (call for help and perform concurrently)
   - give 0.5 mL of 1:1,000 epinephrine IM to lateral thigh (0.01 mL/kg up to 0.4 mL for children)
   - remove causative agent if possible
   - otherwise, provide 100% O₂ through mask, give bolus 1,000 mL (20 mL/kg for children)
   - have continuous pulse oximetry and telemetry monitoring
   - frequently monitor BP
2. secondary treatment
   - diphenhydramine (Benadryl®) 50 mg IM or IV q4-6h
   - methylprednisolone 50-100 mg IV (dose depending on severity)
   - salbutamol (Ventolin®) via nebulizer if bronchospasm

Disposition

- monitor for 4-6 h in ED (minimum) and arrange follow-up with family physician in 24-48 h
- can have second phase (biphasic) reaction up to 48 h later, patient may need to be supervised (oral steroids on discharge may prevent this)
- educate patient on avoidance of allergens
- 3-day course of:
  - H₁ antagonist (cetirizine 10 mg PO OD or Benadryl® 50 mg PO q4-6h)
  - H₂ antagonist (ranitidine 150 mg PO OD)
  - corticosteroid (prednisone 50 mg PO OD) generally given for 5 d

Asthma

- see Respiriology, R7
- chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction

Investigations

- O₂ saturation
- peak flow meter
- ± ABG if in severe respiratory distress
- CXR if diagnosis in doubt or concerns of pneumonia, pneumothorax, etc.
### Table 15. Asthma Assessment and Management

<table>
<thead>
<tr>
<th>Classifications</th>
<th>History and Physical Exam</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Arrest</td>
<td>• Exhausted, confused, diaphoretic, cyanotic&lt;br&gt;• Silent chest, ineffective respiratory effort&lt;br&gt;• Decreased HR, RR&gt;30, pCO2&gt;45 mmHg&lt;br&gt;• O2 sat &lt;90% despite supplemental O2</td>
<td>• 100% O2, cardiac monitor, IV access&lt;br&gt;• Intubate (consider induction with ketamine)&lt;br&gt;• β-agonist: nebulizer 5 mg continually&lt;br&gt;• Anticholinergics: nebulizer 0.5 mg x 3&lt;br&gt;• IV steroids: methylprednisolone 125 mg</td>
</tr>
<tr>
<td>Imminent</td>
<td></td>
<td>• Anticipate need for intubation&lt;br&gt;• Similar to above management&lt;br&gt;• Magnesium sulphate 2 g IV&lt;br&gt;• O2 to achieve O2 sat &gt;92%</td>
</tr>
<tr>
<td>Severe Asthma</td>
<td>• Agitated, diaphoretic, labored respirations&lt;br&gt;• Speaking in words&lt;br&gt;• No relief from β-agonist&lt;br&gt;• O2 sat &lt;90%, FEV1 &lt;50%</td>
<td>• β-agonist: MDI or nebulizer q5min&lt;br&gt;• Steroids: prednisone 40-60 mg PO&lt;br&gt;• Anticholinergics (Atrovent) MDI or nebulizer x3</td>
</tr>
<tr>
<td>Moderate Asthma</td>
<td>• SOB at rest, cough, congestion, chest tightness&lt;br&gt;• Speaking in phrases&lt;br&gt;• Inadequate relief from β-agonist&lt;br&gt;• FEV1 50-80%</td>
<td>• O2 to achieve O2 sat &gt;92%&lt;br&gt;• β-agonist: MDI regular use (2-4 puffs q2-4h) until symptoms controlled, then prn&lt;br&gt;• prednisone 30-60 mg/d for 7-14 d with no taper&lt;br&gt;• counsel on medication adherence&lt;br&gt;• inhaled corticosteroids if not already prescribed&lt;br&gt;• follow-up with primary care physician</td>
</tr>
<tr>
<td>Mild Asthma</td>
<td>• Exertional SOB/cough with some nocturnal symptoms&lt;br&gt;• Difficulty finishing sentences&lt;br&gt;• FEV1 &gt;80%</td>
<td>• β-agonist: nebulizer 0.5 mg x 3&lt;br&gt;• Monitor FEV1&lt;br&gt;• Consider steroids (MDI or PO)</td>
</tr>
</tbody>
</table>

### Disposition
- β-agonist MDI regular use (2-4 puffs q2-4h) until symptoms controlled, then prn
- prednisone 30-60 mg/d for 7-14 d with no taper
- counsel on medication adherence
- inhaled corticosteroids if not already prescribed
- follow-up with primary care physician

### Cardiac Dysrhythmias

- see Cardiology and Cardiac Surgery, C15

#### Bradydysrhythmias and AV Conduction Blocks
- AV conduction blocks
  - 1st degree: prolonged PR interval (>200 msec), no treatment required
  - 2nd degree
    - Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - Mobitz II: PR interval constant with dropped QRS complex, can progress to 3rd degree AV block
  - 3rd degree: P wave unrelated to QRS complex, PP and RR intervals constant
    - atropine and transcutaneous pacemaker (atropine with caution)
    - if transcutaneous pacemaker fails consider dopamine, epinephrine IV
    - long-term treatment for Mobitz II and 3rd degree block – internal pacemaker
- sinus bradycardia (rate <60 bpm)
  - can be normal (especially in athletes)
  - causes: vagal stimulation, vomiting, myocardial infarction/ischemia, increased ICP, sick sinus node, hypothyroidism, drugs (e.g. β-blockers, CCBs)
  - treat if symptomatic (hypotension, chest pain)
    - acute: atropine ± transcutaneous pacing
    - sick sinus: transcutaneous pacing
    - drug induced: discontinue/reduce offending drug

#### Supraventricular Tachydysrhythmias (narrow QRS)
- sinus tachycardia (rate >100 bpm)
  - causes: increased sympathetic tone, drugs, fever, hypotension, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause, consider β-blocker if symptomatic
- regular rhythm
  - vagal maneuvers (carotid massage, Valsalva), adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once
  - rhythm converts: probable re-entry tachycardia (AVNRT more common than AVRT)
    - monitor for recurrence
    - treat recurrence with adenosine or longer acting medications
  - rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
    - rate control (diltiazem, β-blockers) and consult cardiology
- irregular rhythm
  - probable atrial fibrillation, atrial flutter, or multifocal atrial tachycardia
    - rate control (diltiazem, β-blockers)
**Atrial Fibrillation**
- most common sustained dysrhythmia; no organized P waves (atrial rate >300/min), irregularly irregular heart rate, narrow QRS (typically)
- etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, sick sinus syndrome
- treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
- decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
- acute management
  - if unstable: immediate synchronized cardioversion
  - if onset of A Fib is >48 h: rate control, anticoagulate 3 wk prior to and 4 wk after cardioversion or do transesophageal echocardiogram to rule out clot
  - if onset <48 h: may cardiovert
    - electrical cardioversion: synchronized direct current (DC) cardioversion
    - chemical cardioversion: procainamide, flecainide, propafenone
- long-term management: rate or rhythm control, consider anticoagulation (CHADS2 score, see Cardiology and Cardiac Surgery, C19)

**Ventricular Tachydysrhythmias (wide QRS)**
- VTach (rate usually 140-200 bpm)
  - definition: 3 or more consecutive ventricular beats at >100 bpm
  - etiology: CAD with MI is most common cause
  - treatment: sustained VTach (>30 s) is an emergency
    - no hemodynamic compromise: synchronized DC cardioversion
    - hemodynamic compromise: synchronized DC cardioversion, lidocaine, amiodarone, procainamide
- ventricular fibrillation: call a code blue, follow ACLS for pulseless arrest
- torsades de points
  - looks like VTach but QRS ‘rotates around baseline’ with changing axis and amplitude (twisted ribbon)
  - etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
  - treatment:
    - IV MgSO4, temporary overdrive pacing, isoproterenol
    - correct cause of prolonged QT

**Chronic Obstructive Pulmonary Disease**
- see Respirology, R9
  - progressive development of irreversible airway obstruction, typically caused by smoking
  - acute exacerbation: episode of increased dyspnea, coughing, increase in sputum volume or purulence

**History and Physical Exam**
  - worsening dyspnea or tachypnea
  - acute change in frequency, quantity, and color of sputum production
  - triggers: pneumonia, urinary tract infection, PE, CHF, MI, drugs

**Investigations**
- CBC, electrolytes, ABG, CXR, ECG, PFTs

**Management**
- keep O2 sat 88-92% (be aware when giving O2 to chronic hypercapnic/CO2 retainers but do not withhold O2 if hypoxic)
- apply BiPAP if severe distress, arterial pH <7.35, or hypercapnic
- ipratropium is anticholinergic agent of choice, add salbutamol
- steroids: ipratropium 40 mg PO for 5 d
- antibiotics: TMP-SMX, cephalosporins, respiratory quinolones (if acute change in frequency, quantity, and color of sputum production)
- if life-threatening, ICU admission for ventilation (chance of ventilation dependency)
- lower threshold to admit if comorbid illness

**Disposition**
- can use up to 4-6 puffs qid of ipratropium and salbutamol for exacerbations
- continue antibiotics if started and give tapering steroids
**Congestive Heart Failure**

- **Etiology**
  - decreased myocardial contractility: ischemia, infarction, cardiomyopathy, myocarditis
  - pressure overload states: HTN, valve abnormalities, congenital heart disease
  - restricted cardiac output: myocardial infiltrative disease, cardiac tamponade
  - volume overload

- **Presentation**
  - left-sided heart failure
    - dyspnea, decreased exercise tolerance, paroxysmal nocturnal dyspnea, orthopnea, nocturia, fatigue, possibly altered mental status, syncope, angina, systemic hypotension
  - hypoxia, decreased air entry to lungs, rales, S3 or S4, pulmonary edema on CXR, pleural effusion (usually right sided)
  - right-sided heart failure
    - dependent bilateral pitting edema, JVP elevation, hepatic enlargement, ascites
  - patients often present with a combination of right-sided and left-sided symptoms

- **Investigations**
  - labs: CBC, electrolytes, AST, ALT, bilirubin, Cr, BUN, cardiac enzymes, brain natriuretic peptide
  - CXR (see sidebar, ER32)
  - ECG: look for MI, ischemia (ST elevation/depression, T-wave inversion)
    - in CHF: LVH, atrial enlargement, conduction abnormalities
  - ABG: if severe or refractory to treatment
    - hypoxemia, hypercapnia and acidosis are signs of severe CHF
  - echocardiogram: not usually used in emergency evaluation, previous results may aid in diagnosis
  - may be precipitated by dysrhythmia (e.g. sudden onset AFib) – correct if new
  - rule out serious differentials such as PE, pneumothorax, pneumonia/empyema, COPD exacerbation

- **Management (acute)**
  - ABC, may require intubation if severe hypoxia
  - sit upright, cardiac monitoring and continuous pulse oximetry
  - saline lock IV, Foley catheter (to follow effectiveness of diuresis)
  - 100% O₂ by mask
    - if poor response, may require BiPAP or intubation
  - drugs
    - nitroglycerin 0.3 mg SL q5min prn ± topical nitroglycerine patch (0.2-0.8 mg/h)
      - if not responding or ischemia: 10-200 µg/min IV, titrate
    - diuretic if volume overloaded (e.g. furosemide 40-80 mg IV), use caution if cause is valvulopathy
    - morphine 1-2 mg IV prn
      - if hypotensive: dobutamine (2.5 µg/kg/min IV) or dopamine (5-10 µg/kg/min IV), titrate up to sBP 90-100 mmHg
    - ASA 160 mg chew and swallow
    - treat precipitating factor
    - cardiology or medicine consult

**Deep Vein Thrombosis and Pulmonary Embolism**

- **Risk Factors**
  - Virchow’s triad
    - alterations in blood flow (venous stasis)
    - injury to endothelium
    - hypercoagulable state (including pregnancy, use of OCP, malignancy)
  - clinical risk factors

- **Presentation**
  - DVT: calf pain, leg swelling/erythema/edema, palpable cord on exam; can be asymptomatic
  - PE: dyspnea, pleuritic chest pain, hemoptysis, tachypnea, cyanosis, hypoxia, fever
  - clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT/PE; investigation often needed
  - calculate the PERC (PE rule out criteria) score to assess the need for PE workup before assessing the likelihood of a PE (Wells’ Criteria)
Investigations
- ECG and CXR are useful to look for other causes (e.g., ACS, pneumonia)
- D-dimer is only useful if it is negative in low risk patients (highly sensitive)
- U/S has high sensitivity and specificity for proximal clot but only 73% sensitivity for DVT below the knee (may need to repeat in 1 wk)
- CT angiography has high sensitivity and specificity for PE, may also suggest other etiologies
- V/Q scan useful when CT angiography not available, or patient unable to tolerate IV contrast (e.g., renal failure, allergy)

Management of DVT/PE
- LMWH unless patient also has renal failure
  - dalteparin 200 IU/kg SC q24h or enoxaparin 1.5 mg/kg SC q24h
- warfarin started at same time as LMWH (5 mg PO OD initially)
- LMWH discontinued when INR has been therapeutic (2-3) for 2 consecutive days
  - early ambulation with analgesia is safe if appropriately anticoagulated
- rivaroxaban can be used in both acute management of symptomatic DVT or PE and extended treatment
  - 15 mg PO bid for first 21 days; 20 mg PO daily for remaining treatment (taken with food at approximately the same time each day)
- IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
- consider thrombolysis if extensive DVT or PE causing hemodynamic compromise
- often can be treated as outpatient, may require analgesia for chest pain (narcotic or NSAID)
- admit if hemodynamically unstable, require supplemental O2, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy
- consider referral to medicine for coagulopathy and malignancy workup
- long-term anticoagulation
  - if reversible risk factor: 3-6 mo of warfarin
  - idiopathic VTE: may need longer term warfarin (5 yr or more)

**Figure 12. Approach to suspected DVT**

**Figure 13. Approach to suspected PE**
**Diabetic Emergencies**

- see Endocrinology, E11

**Diabetic Ketoacidosis**
- severe insulin deficiency resulting in hyperglycemia (200-1,000 mg/dL), dehydration, and electrolyte abnormalities
- history and physical exam – often young, type 1 DM, may be first presentation of undiagnosed DM (may occur in small percentage of type 2 DM patients)
- early symptoms: polyuria, polydipsia, malaise, nocturia, weight loss
- late signs and symptoms
  - anorexia, N/V, dyspnea (often due to acidosis), fatigue
  - abdominal pain
  - drowsiness, stupor, coma
  - Kussmaul’s respiration
  - fruity acetone breath
- investigations
  - CBC, glucose, electrolytes, BUN/Cr, Ca²⁺, Mg²⁺, PO₄³⁻, urine glucose and ketones
  - ABG
  - ECG (MI possible precipitant; electrolyte disturbances may predispose to dysrhythmia)
- management
  - rehydration
    - bolus of NS, then high rate NS infusion (be aware of overhydration and cerebral edema, especially in pediatric patients)
    - beware of a pseudohyponatremia due to hyperglycemia (add 3 Na⁺ per 18 glucose over 100 mg/dL)
  - potassium
    - essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial K⁺ <5.5 mEq/L)
    - use cardiac monitoring if potassium levels normal or low
  - insulin
    - critical, as this is the only way to turn off gluconeogenesis/ketosis
    - do not give insulin if K⁺ <3.3 mEq/L
    - initial bolus of 5-10 U short-acting/regular insulin (or 0.2 U/kg) IV in adults (controversial – may just start with infusion)
    - followed by continuous infusion at 5-10 U (or 0.1 U/kg) per h
    - add D5W to IV fluids when blood glucose <270 mg/dL to prevent hypoglycemia
  - bicarbonate is not given unless patient is at risk of death or shock (typically pH <7.0)

**Hyperosmolar Hyperglycemic State**
- state of extreme hyperglycemia (800-2,400 mg/dL) due to relative insulin deficiency, increased counter- regulatory hormones, gluconeogenesis, and dehydration (due to osmotic diuresis) in type 2 DM, high mortality (5-20%)
- history and physical exam
  - mental disturbances, coma, delirium, seizures
  - polyuria
  - N/V
- investigations
  - CBC, electrolytes, Cr, BUN, glucose, Mg²⁺, PO₄³⁻, urine glucose and ketones
  - ABG
  - ECG
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O₂ and cardiac monitoring, frequent electrolyte and glucose monitoring
  - insulin as required
  - identify and treat precipitant if present (the 5 Is)
**Hypoglycemia**
- very common ED presentation
- history and physical exam
  - last meal, known DM, prior similar episodes, drug therapy and compliance
  - liver/renal/endocrine/neoplastic disease
  - depression, alcohol or drug use
- management
  - IV access and rapid blood glucose measurement
  - D50W 50 mL IV push, glucose PO if mental status permits
  - O₂, cardiac, frequent blood glucose monitoring
  - thiamine 100 mg IM
  - full meal as soon as mental status permits
  - if episode due to long-acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long t₁/₂ (may require admission for monitoring)
  - search for cause (most often due to exogenous insulin, alcohol, or sulfonylureas)

**Electrolyte Disturbances**
- see Nephrology, NP7 and Endocrinology, E38

**Table 16. Electrolyte Disturbances**

<table>
<thead>
<tr>
<th>Electrolyte Disturbance</th>
<th>Common Causes</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypernatremia</td>
<td>Inadequate H₂O intake (elderly/disabled) or inappropriate excretion of H₂O (diuretics, Li, and DI)</td>
<td>Lethargy, weakness, irritability, and edema; seizures and coma occur with severe elevations of Na⁺ levels (&gt;158 mEq/L)</td>
<td>Salt restrict and give free water</td>
<td>No more than 12 mEq/L in 24 h drop in Na⁺ (0.5 mEq/L/h) due to risk of cerebral edema, seizures, death</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Hypo-osmolar (dilutional e.g. CHF, cirrhosis, ascites) and hyper-osmolar (usually glucose)</td>
<td>Acute: Neurologic symptoms 2º to cerebral edema, headache, decreased LOC, depressed reflexes</td>
<td>Water restrict</td>
<td>Limit total rise to 8 mEq/L in 24 h (0.5 mEq/L/h maximum) as patients are at risk of central pontine myelinolysis</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Rhabdomyolysis, insulin deficiency, metabolic acidosis</td>
<td>Nausea, palpitations, muscle stiffness, areflexia</td>
<td>Protect heart: calcium gluconate Shift K⁺ into cells: insulin, NaHCO₃, salbutamol</td>
<td>ECG: peaked/narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, AV block, ventricular fibrillation</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Metabolic alkalosis, insulin, diuretics, anorexia, salbutamol</td>
<td>N/V, fatigue, muscle cramps, constipation</td>
<td>K-Dur™, K⁺ sparing diuretics, IV solutions with 20-40 mEq/L over 3-4 h</td>
<td>ECG: U waves most important, flattened/inverted T waves, prolonged QT, depressed ST May need to restore Mg²⁺</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Hyper-PTH and malignancy account for ~90% of cases</td>
<td>Multisystem including CVS, GI (gastrointestinal), renal (stones), rheumatological, MSK (bones), psychiatric (mood)</td>
<td>Isotonic saline + furosemide if hypervolemic Bisphosphonates, dialysis, chelation (EDTA or oral PO₄³⁻)</td>
<td>Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>iatrogenic, low Mg²⁺, liver dysfunction, 1º hypo-PTH</td>
<td>Laryngospasm, hyperreflexia, paresthesia, tetany, Chvostek’s and Trousseau’s sign</td>
<td>Acute (ionized Ca²⁺ &lt;2.8 mg/dL) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion</td>
<td>Prolonged QT interval can arise, leading to dysrhythmia as can upper airway obstruction</td>
</tr>
</tbody>
</table>

**Hypertensive Emergencies**

**Hypertensive Emergency (Hypertensive Crisis)**

**Etiology**
- essential HTN, emotional exertion, pain, use of sympathomimetic drugs (cocaine, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), pheochromocytoma, pregnancy

**Presentation**
- elevation of systolic and diastolic BP (irrespective of BP) with acute end-organ damage (CNS, renal, CVS, retinal)
Table 17. Signs and Symptoms of Hypertensive Emergencies

<table>
<thead>
<tr>
<th>Complication</th>
<th>CNS</th>
<th>Retinal</th>
<th>Renal</th>
<th>Cardiac</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA,</td>
<td>Stroke,</td>
<td>Vision change,</td>
<td>Nocturia, elevated</td>
<td>Ischemia/angina,</td>
<td>N/V, abdominal</td>
</tr>
<tr>
<td>headache,</td>
<td>headache,</td>
<td>hemorhage,</td>
<td>Cr, proteinuria,</td>
<td>infarct, dissection</td>
<td>pain, elevated</td>
</tr>
<tr>
<td>altered mental</td>
<td>altered mental</td>
<td>excudates,</td>
<td>hematura, oliguria</td>
<td>(back pain), CHF</td>
<td>liver enzymes</td>
</tr>
<tr>
<td>status, seizures, hemorrhage</td>
<td>status, seizures,</td>
<td>papilledema</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigations

- CBC, electrolytes, BUN, Cr, U/A
- peripheral blood smear: to detect microangiopathic hemolytic anemia
- CXR: if SOB or chest pain
- ECG, troponins, CK if chest pain
- CT head: if neurological findings or severe headache
- toxicology screen if sympathomimetic overdose suspected

Management

- in general, the strategy for management is to gradually and progressively reduce BP in 24-48 h
- lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually nitroprenus and labetolot) or adjusting antihypertensive
- if preeclampsia, immediately consult OB/GYN (see Obstetrics, OB15)
- if transfer to ICU for further reduction in BP under monitored setting
- in case of ischemic stroke: do not rapidly reduce BP maintain BP >150/100 for 5 d
- in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
- in case of excessive catecholamines: avoid β-blockers (except labetolot)
- in case of ACS: address ischemia initially, then BP

Hypertensive Urgency

- definition: severely elevated BP (usually sBP >180, dBP >115) with no evidence of end-organ damage
- most commonly due to non-adherence with medications
- most commonly due to non-adherence with medications
- treatment: initiate/adjust antihypertensive therapy, monitor in ED (up to 6 h) and discharge with follow up for 48-72 h
- goal: differentiate hypertensive emergencies from hypertensive urgencies

Table 18. Most Commonly Used Agents for the Treatment of Hypertensive Crisis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Adverse Effects*</th>
<th>Special Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Nitroprusside</td>
<td>0.25-10 µg/kg/min</td>
<td>Immediate</td>
<td>3-5 min</td>
<td>N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome</td>
<td>Most hypertensive emergencies (especially CHF, aortic dissection) Use in combination with β-blockers (e.g. esmolol) in aortic dissection Caution with high ICP and azotemia</td>
</tr>
<tr>
<td>Nicardipine (CCB)</td>
<td>2 mg IV bolus, then 4 mg/kg/h IV</td>
<td>15-30 min</td>
<td>40 min</td>
<td>Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, RF, eclampsia, sympathetic crisis)</td>
<td>Most hypertensive emergencies Caution with acute CHF</td>
</tr>
<tr>
<td>Fensolodan Meylotate (dopamine receptor antagonist)</td>
<td>0.05-0.1 µg/kg/min IV</td>
<td>&lt;5 min</td>
<td>8-10 min</td>
<td>Tachycardia, headache, nausea, flushing (e.g. acute RF)</td>
<td>Most hypertensive emergencies Caution with glaucoma</td>
</tr>
<tr>
<td>Enalapril (ACEI)</td>
<td>0.625-1.25 mg IV q6h</td>
<td>15-30 min</td>
<td>12-24 h</td>
<td>Theoretical fall in pressure in high renin states not seen in studies</td>
<td>Acute LV failure Avoid in acute MI, pregnancy, acute RF</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-20 µg/min IV</td>
<td>1-2 min</td>
<td>3-5 min</td>
<td>Hypotension, bradycardia, headache, lightheadedness, dizziness</td>
<td>MI/pulmonary edema</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5-10 mg IV/IM q20min (max 20 mg)</td>
<td>5-20 min</td>
<td>2-6 h</td>
<td>Dizziness, drowsiness, headache, tachycardia, Na⁺ retention</td>
<td>Eclampsia</td>
</tr>
</tbody>
</table>
Table 18. Most Commonly Used Agents for the Treatment of Hypertensive Crisis (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Adverse Effects*</th>
<th>Special Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADRENERGIC INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>20 mg IV bolus q10min or 0.5-2 mg/min</td>
<td>5-10 min</td>
<td>3-6 h</td>
<td>Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension</td>
<td>Most hypertensive emergencies (especially eclampsia) Avoid in acute CHF, heart block &gt; 1st degree</td>
</tr>
<tr>
<td>Esmolol</td>
<td>250-500 µg/kg/min 1 min, then 50 µg/kg/min for 4 min; repeat</td>
<td>1-2 min</td>
<td>10-20 min</td>
<td>Hypotension, nausea, bronchospasm</td>
<td>Aortic dissection, acute MI SVT dysrhythmias, perioperative HTN Avoid in acute CHF, heart block &gt; 1st degree</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>5-15 mg q5-15min</td>
<td>1-2 min</td>
<td>3-10 min</td>
<td>Tachycardia, headache, flushing</td>
<td>Catecholamine excess (e.g. pheochromocytoma)</td>
</tr>
</tbody>
</table>

*Hypotension may occur with all of these agents

Stroke

- see Neurology, N47
- can be ischemic (80% of all strokes) or hemorrhagic

Presentation

- sudden onset persisting neurological deficits

Table 19. Signs and Symptoms of Stroke

<table>
<thead>
<tr>
<th>Signs/ Symptoms</th>
<th>General</th>
<th>Language/ Throat</th>
<th>Vision</th>
<th>Coordination</th>
<th>Motor</th>
<th>Sensation</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased LOC, changed mental status, confusion, neglect</td>
<td>Decreased LOC, confused</td>
<td>Dyssarhnia, aphasia, swallowing difficulty</td>
<td>Diplopia, eye deviation, asymmetric pupils, visual field defect</td>
<td>Ataxia, intention tremor, lack of coordination</td>
<td>Increased tone, loss of power, spasticity</td>
<td>Loss of sensation</td>
<td>Hyper-reflexia, clonus</td>
</tr>
</tbody>
</table>

- patients with hemorrhagic stroke can present with sudden onset thunderclap headache that is usually described as "worst headache of my life"
- constellation of neurological deficits can point to certain vascular territories
- stroke mimics: seizure, migraine, hypoglycemia, Todd’s paralysis, peripheral nerve injury, Bell’s palsy, tumor, syncope

Table 20. Stroke Syndromes

<table>
<thead>
<tr>
<th>Region of Stroke</th>
<th>Stroke Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Cerebral Artery</td>
<td>Primarily frontal lobe function affected</td>
</tr>
<tr>
<td></td>
<td>Alteration mental status, impaired judgment, contralateral lower extremity weakness and hypoesthesia, gait apraxia</td>
</tr>
<tr>
<td>Middle Cerebral Artery</td>
<td>Contralateral hemiparesis (arm and hand weakness &gt; leg weakness) and hypoesthesia, ipsilateral hemianopia, gaze preference to side of lesion ± agnosia, receptive/expressive aphasia</td>
</tr>
<tr>
<td>Posterior Cerebral Artery</td>
<td>Affects vision and thought</td>
</tr>
<tr>
<td></td>
<td>Homonymous hemianopia, cortical blindness, visual agnosia, altered mental status, impaired memory</td>
</tr>
<tr>
<td>Vertebralbasilar Artery</td>
<td>Wide variety of cranial nerve, cerebellar, and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dyssarhnia, facial hypoesthesia, syncope, ataxia</td>
</tr>
<tr>
<td></td>
<td>Loss of pain and temperature sensation in ipsilateral face and contralateral body</td>
</tr>
</tbody>
</table>

Investigations

- CBC, electrolytes, blood glucose, coagulation studies ± cardiac biomarkers ± toxicology screen
- non-contrast CT head: look for hemorrhage, ischemia
- ECG ± echocardiogram: rule out atrial fibrillation, acute MI as source of emboli
- other imaging: carotid dopplers, CTA, MRA as appropriate

Exclusion Criteria for tPA:

- Suspected subarachnoid hemorrhage
- Previous intracranial hemorrhage
- Cerebral infarct or severe head injury within the past 3 mo
- Recent pericarditis
- Major surgery within the past 14 d
- Recent LP or arterial puncture at noncompressible site
- Patient is pregnant
- BP >185 mmHg systolic, or >110 mmHg diastolic
- Bleeding diathesis
- Prolonged PTT (more than 40 s) or INR >1.4
- Platelet count <100,000
- Blood glucose <50 or >400 mg/dL
- Intracranial hemorrhage on CT or large volume infarct
- Seizure at onset causing deficit
- Previously ADL dependent (clinical judgment)

Differentiation of UMN Disease vs. LMN Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>UMN Disease</th>
<th>LMN Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle deficit Reflexes</td>
<td>Increased</td>
<td>Decreased/absent</td>
</tr>
<tr>
<td>Tone</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Absent/minimal</td>
<td>Upgoing</td>
</tr>
<tr>
<td>Babinski</td>
<td>Upgoing</td>
<td>Downgoing</td>
</tr>
</tbody>
</table>
Management

- Thrombolysis: immediate assessment for eligibility; need acute onset, <4.5 h from drug administration time AND compatible physical findings AND normal CT with no bleed
- Intubation with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protection reflexes
- Elevating head of bed if risk of elevated ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV ± cardiac monitoring
  - Judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischemic penumbra)
  - BP control: only treat severe HTN (sBP >200, dBP >120, mean arterial BP >140) or HTN associated with hemorrhagic stroke transformation, cardiac ischemia, aortic dissection, or renal damage; use IV nitroprusside or labetalol
  - Glycemic control: keep fasting glucose <117 mg/dL in acute phase (5 d)
- Cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- Consult neurosurgery, neurology, medicine as indicated

Medications

- Acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 4.5 h of symptom onset with no evidence of hemorrhage on CT scan
- Antiplatelet agents: prevent recurrent stroke or stroke after TIAs, e.g. Aspirin® (1st line); clopidogrel, Aggrenox® (2nd line)
- Anticoagulation: DVT prophylaxis if immobile; treat atrial fibrillation if present

Gynecologic/Urologic Emergencies

Vaginal Bleeding

- See Gynecology, GY6 and Obstetrics, OB21

Etiology

- Pregnant patient
  - 1st/2nd trimester pregnancy: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause)
  - 2nd/3rd trimester pregnancy: placenta previa, placental abruption, premature rupture of membranes, preterm labor
  - Other: trauma, bleeding cervical polyp, passing of mucous plug
- Postpartum
- Postpartum hemorrhage, uterine inversion, retained placental tissue, endometritis
- Non-pregnant patients
  - Dysfunctional uterine bleeding, uterine fibroids, pelvic tumors, trauma, endometriosis, PID, exogenous hormones

History

- Characterize bleeding (frequency, duration, number of pads/tampons, cyclicity)
- Pain, if present (OPQRSTU)
- Menstrual history, sexual history, STD history, syncope/pre-syncope
- Details of pregnancy, including gush of fluid and fetal movement (>20 wk)

Physical Exam

- ABC (especially noting postural BP/HR and mucous membrane)
- Abdominal examination (peritoneal signs, tenderness, distention, mass)
- Speculum examination (NOT IF 2nd/3rd trimester bleeding; perform only when placenta previa is ruled out with U/S)
  - Look for active bleeding, trauma/anomaly, and cervical dilatation
  - Use sterile speculum if pregnant
- Bimanual examination (cervical tenderness, size of uterus, cervical length/dilatation)
  - Sterile gloves if pregnant

Investigations

- β-hCG test for all patients with childbearing potential
- CBC, blood and Rh type, quantitative β-hCG, PTT, INR
- Type and cross if significant blood loss
- Transvaginal U/S (rule out ectopic pregnancy and spontaneous abortion)
- Abdominal U/S (rule out placenta previa and fetal demise)
- Postpartum
  - U/S for retained products
  - β-hCG if concerned about retained tissue

7 Causes of Emboli from the Heart

- Atrial fibrillation
- MI
- Endocarditis
- Valvular disease
- Dilated cardiomyopathy
- Left heart myxoma
- Prosthetic valves

Vaginal bleeding can be life-threatening. Always start with ABCs and ensure your patient is stable.
Vaginal bleeding (and its underlying causes) can be a very distressing event for patients; ensure appropriate support is provided.

Need β-hCG ≥1,200 to see intrauterine changes on transvaginal U/S
An ectopic pregnancy can be ruled out by confirming an intrauterine pregnancy by bedside U/S unless the patient is using IVF.
Management

- **ABCs**
- pulse oximeter and cardiac monitors if unstable
- Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
- 1st/2nd trimester pregnancy
  - ectopic pregnancy: definitive treatment with surgery or methotrexate
  - intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
  - U/S indeterminate or β-hCG >1,000-2,000 IU: further workup and/or gynecology consult
  - abortions: if complete, discharge if stable; for all others, acquire gynecology consult
- 2nd/3rd trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
- postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type and cross 4 units of blood, consult OB/GYN immediately
- non-pregnant
  - dysfunctional uterine bleeding (prolonged or heavy flow ± breakthrough bleeding and without ovulation, a diagnosis of exclusion)
    - <35-40 yr of age: Provera® 10 mg PO OD x 10 d, warn patient of a withdrawal bleed, discharge if stable
    - if unstable, admit for IV hormonal therapy, possible D&C
    - >35-40 yr of age: uterine sampling necessary prior to initiation of hormonal treatment to rule out endometrial cancer, U/S for any masses felt on exam
    - tranexamic acid (Cyklokapron®) to stabilize clots
  - structural abnormalities: fibroids or uterine tumors may require excision for diagnosis/treatment, U/S for workup of other pelvic masses, Pap smear/biopsy for cervical lesions

Disposition

- the decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult gynecology for admitted patients
- if patient can be safely discharged, ensure follow up with family physician or gynecologist
  - instruct patient to return to ED for increased bleeding, presyncope

Pregnant Patient in the ED

Table 21. Complications of Pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Fetal</th>
<th>Maternal</th>
</tr>
</thead>
<tbody>
<tr>
<td>First 1-12 wk</td>
<td>Pregnancy failure</td>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td></td>
<td>Spontaneous abortion</td>
<td>Anemia</td>
</tr>
<tr>
<td></td>
<td>Fetal demise</td>
<td>Hyperemesis gravidarum</td>
</tr>
<tr>
<td></td>
<td>Gestational trophoblastic disease</td>
<td>UTI/pyelonephritis</td>
</tr>
<tr>
<td>Second 13-27 wk</td>
<td>Disorders of fetal growth</td>
<td>Gestational DM</td>
</tr>
<tr>
<td></td>
<td>IUGR</td>
<td>Rh incompatibility</td>
</tr>
<tr>
<td></td>
<td>Oligo/polyhydramnios</td>
<td>UTI/pyelonephritis</td>
</tr>
<tr>
<td>Third 28-41 wk</td>
<td>Vasa previa</td>
<td>Preterm labor/PPROM</td>
</tr>
<tr>
<td></td>
<td>Placenta previa</td>
<td>Preeclampsia/eclampsia</td>
</tr>
<tr>
<td></td>
<td>Placental abruption</td>
<td>Placenta previa</td>
</tr>
<tr>
<td></td>
<td>Uterine rupture</td>
<td>Placental abruption</td>
</tr>
<tr>
<td></td>
<td>DVT</td>
<td>Placenta previa</td>
</tr>
</tbody>
</table>

Nephrolithiasis (Renal Colic)

- see Urology, U16

Epidemiology and Risk Factors

- 10% of population (twice as common in males)
- recurrence 50% at 5 yr
- peak incidence 30-50 yr of age
- 75% of stones <5 mm pass spontaneously within 2 wk, larger stones may require consultation

Clinical Features

- urinary obstruction → upstream distention of ureter or collecting system → severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- writhing, never comfortable, N/V, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis
- peritoneal findings/anterior abdominal tenderness usually absent

Kidney Stones

- 80% Calcium oxalate
- 10% Struvite
- 10% Uric acid

Classifying Miscarriage (Abortion)

- Missed: non-viable intrauterine pregnancy
- Threatened: viable intrauterine pregnancy with os closed
- Inevitable: os opened, no products of conception passed
- Incomplete: products of conception partially expelled
- Complete: products of conception completely expelled
- Septic: any of above with presence of infection (usually incomplete)
- Recurrent: >3 spontaneous abortions (recurrent pregnancy loss)
Differential Diagnosis of Renal Colic

- acute ureteric obstruction
- acute abdomen: biliary, bowel, pancreas, AAA
- gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1): herpes zoster, nerve root compression

Investigations

- screening
  - CBC → elevated WBC in presence of fever suggests infection
  - electrolytes, Cr, BUN → to assess renal function
  - U/A: R&M (WBCs, RBCs, crystals), C&S
- imaging
  - non-contrast spiral CT is the study of choice
  - abdominal U/S may demonstrate stone or hydronephrosis (consider in females of childbearing age)
  - AXR will identify large radioopaque stones (calcium, struvite, and cystine stones), but may miss smaller stones, uric acid stones, or stones overlying bony structures; consider as an initial investigation in patients who have a history of radioopaque stones and similar episodes of acute flank pain (CT necessary if film is negative)
- strain all urine → stone analysis

Management

- analgesics: NSAIDs (usually ketorolac [Toradol®], preferable over opioids), antiemetics, IV fluids
- urology consult may be indicated, especially if stone >5 mm, or if patient has signs of obstruction or infection
- α-blocker (e.g. tamsulosin) helpful to increase stone passage in select cases

Disposition

- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and is able to tolerate oral medications
- may advise hydration and limitation of protein, sodium, oxalate, and alcohol intake

Ophthalmologic Emergencies

- see Ophthalmology, OP5, OP42

History and Physical Exam

- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital x-rays, U/S, or CT scan to exclude presence of intraocular metallic foreign body
- visual acuity in both eyes, pupils, extraocular structures, fundoscopy, tonometry, slit lamp exam

Management of Ophthalmologic Foreign Body

- copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab or sterile needle
- antibiotic drops qid until healed
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only
- consider tetanus prophylaxis
- ophthalmology consult if globe penetration suspected

Table 22. Differential Diagnosis of Red Eye in the Emergency Department

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Serious Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light sensitivity</td>
<td>Iritis, keratitis, abrasion, ulcer</td>
</tr>
<tr>
<td>Unilateral</td>
<td>Above + herpes simplex, acute angle closure glaucoma</td>
</tr>
<tr>
<td>Significant pain</td>
<td>Above + scleritis</td>
</tr>
<tr>
<td>White spot on cornea</td>
<td>Corneal ulcer</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>All of the above</td>
</tr>
<tr>
<td>Non-reactive pupil</td>
<td>Acute glaucoma, iritis</td>
</tr>
<tr>
<td>Copious discharge</td>
<td>Gonococcal conjunctivitis</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>All of the above</td>
</tr>
</tbody>
</table>

Indications for Admission to Hospital

- Intractable pain
- Fever (suggests infection) or other evidence of pyelonephritis
- Single kidney with ureteral obstruction
- Bilateral obstructing stones
- Intractable vomiting
- Compromised renal function

Other Ophthalmologic Emergencies

- Infectious: Red eye, endophthalmitis, hypopyon
- Trauma: Globe rupture, orbital blow-out fractures, corneal injuries, eyelid laceration, hyphema, lens dislocation, retrobulbar hemorrhage
- Painful vision loss: Acute iritis, corneal abrasion, globe rupture, lens dislocation, retrobulbar hemorrhage, optic neuritis, temporal arteritis, endophthalmitis, keratitis
- Painless vision loss: Central retinal vein occlusion, amaurosis fugax, occipital stroke

Contraindications to Pupil Dilation

- Shallow anterior chamber
- Iris-supported lens implant
- Potential neurological abnormality requiring pupillary evaluation
- Caution with CV disease – mydriatics can cause tachycardia
### Table 23. Select Ophthalmologic Emergencies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Signs and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Angle Closure</strong></td>
<td>Unilateral red, painful eye</td>
<td>Ophthalmology consult for laser iridotomy</td>
</tr>
<tr>
<td><strong>Glaucoma</strong></td>
<td>Decreased visual acuity, halos around lights</td>
<td>Topical β-blockers, adrenergics, and cholinergics</td>
</tr>
<tr>
<td></td>
<td>Fixed, mid-dilated pupil</td>
<td>Systemic carbonic anhydrase inhibitors and hyperosmotic agents</td>
</tr>
<tr>
<td></td>
<td>N/V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marked increase in IOP (&gt;40 mmHg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shallow anterior chamber ± cells</td>
<td></td>
</tr>
<tr>
<td><strong>Chemical Burn</strong></td>
<td>Known exposure to acids or alkali (worse)</td>
<td>Irrigate at site of accident</td>
</tr>
<tr>
<td></td>
<td>Pain, decreased visual acuity</td>
<td>IV NS drip in ED with eyelid retracted</td>
</tr>
<tr>
<td></td>
<td>Vascularization or defects of cornea</td>
<td>Swab fornices</td>
</tr>
<tr>
<td></td>
<td>Iris and lens damage</td>
<td>Cycloplegic drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical antibiotics and patching</td>
</tr>
<tr>
<td><strong>Orbital Cellulitis</strong></td>
<td>Red, painful eye, decreased visual acuity</td>
<td>Admission, ophthalmology consult</td>
</tr>
<tr>
<td></td>
<td>Headache, fever</td>
<td>Blood cultures, orbital CT</td>
</tr>
<tr>
<td></td>
<td>Lid erythema, edema, and difficulty opening eye</td>
<td>IV antibiotics (ceftriaxone + vancomycin)</td>
</tr>
<tr>
<td></td>
<td>Conjunctival injection and chemosis</td>
<td>Drainage of abscess</td>
</tr>
<tr>
<td><strong>Retinal Artery Occlusion</strong></td>
<td>Sudden, painless, monocular vision loss</td>
<td>Restore blood flow &lt;2 h</td>
</tr>
<tr>
<td></td>
<td>RAPD</td>
<td>Massage globe</td>
</tr>
<tr>
<td></td>
<td>Cherry red spot and retinal paller on funduscopy</td>
<td>Decrease IOP (topical β-blockers, inhaled O₂/CO₂ mix, IV Diamox®, IV mannitol, drain aqueous fluid)</td>
</tr>
<tr>
<td><strong>Retinal Artery Detachment</strong></td>
<td>Flashes of light, floaters, and curtains of blackness/periocular vision loss</td>
<td>Ophthalmology consult for scleral buckle/ pneumatic retinopex</td>
</tr>
<tr>
<td></td>
<td>Painless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of red reflex, decreased IOP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detached areas are gray ± RAPD</td>
<td></td>
</tr>
</tbody>
</table>

### Dermatologic Emergencies

#### Life-Threatening Dermatoses

**Rash Characteristics**

**A. Diffuse Rashes**

- **SSSS**
  - caused by an exotoxin from infecting strain of coagulase-positive *S. aureus*
  - mostly occurs in children
  - prodrome: fever, irritability, malaise, and skin tenderness
  - sudden onset of diffuse erythema: skin is red, warm, and very tender
  - flaccid bullae that are difficult to see, then desquamate in large sheets
  - Nikolsky’s sign: gentle lateral stroking of skin causes epidermis to separate

- **TEN (≥30% of BSA)**
  - see Dermatology, D21
  - caused by drugs (e.g. phenytoin, sulfas, penicillins, and NSAIDs), bone marrow transplantation, and blood product transfusions
  - usually occurs in adults
  - diffuse erythema followed by necrosis
  - severe mucous membrane blistering
  - entire epidermis desquamation
  - high mortality (>50%)

- **TSS**
  - see Infectious Diseases, ID24
  - caused by superantigen from *S. aureus* or GAS activating T-cell and cytokines
  - patient often presents with onset of shock and multi-organ failure, fever
  - diffuse erythematous macular rash
  - at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, and skin (necrotizing fasciitis, gangrene)

- **vesicobullous lesions**
  - EM
  - see Dermatology, D21
  - immunologic reaction to herpes simplex
  - viral prodrome 1-14 d before rash
  - “target lesion”: central gray bulla or wheal surrounded by concentric rings of erythema and normal skin
SJS (<10% of BSA)
- see Dermatology, D21
- related to drugs such as antiepileptics and biologic agents (e.g. infliximab)
- EM with constitutional symptoms and mucous membrane involvement (milder mucous membrane involvement than TEN)

B. Discrete Lesions
- pyoderma gangrenosum
  - often associated with immunocompromised patients (HIV, leukemia, or lymphoma) with Gram-negative sepsis
  - often occurs in arms, hands, feet, or perineal region
  - usually begins as painless macule-vesicle → pustule/bulla on red/blue base → sloughing, leaving a gangrenous ulcer
- DGI
  - see Dermatology, D31
  - fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), and septic arthritis (in larger joints, such as knees, ankles, and elbows)
  - most commonly in gonococcus positive women during menstruation or pregnancy
  - skin lesions usually appear in extremities and resolve quickly (<7 d)
- meningococcemia
  - flu-like symptoms of headache, myalgia, N/V
  - petechial, macular, or maculopapular lesions with gray vesicular centers
  - usually a few millimeters in size, but may become confluent and hemorrhagic
  - usually appear in extremities, but may appear anywhere
  - look for signs of meningeal irritation: Brudzinski, Kernig, nuchal rigidity, jolt accentuation

History and Physical Exam
- determine onset, course, and location of skin lesions
- fever, joint pain
- associated symptoms: CNS, respiratory, GU, GI, renal, liver, mucous membranes
- medication history
- vitals

Investigations
- immediate consultation if patient unstable
- CBC, electrolytes, Cr, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)

Management
- general: judicious IV fluids and electrolyte control, consider vasopressors if hypotensive, prevention of infection
- determine if admission and consult needed: dermatology or infectious diseases
- specific management is determined by etiology
  - SSSS, TSS, DGI, and meningococcemia
    - IV antibiotics
  - EM, SJS, and TEN
    - stop precipitating medication
    - fluids
    - symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IVIg
    - TEN: debride necrotic tissue

Disposition
- most cases will require urgent care and hospitalization
- TEN: early transfer to burn center improves outcome

Environmental Injuries

Heat Exhaustion and Heat Stroke
- predisposing factors: young persons who overexert themselves, older adults who cannot dissipate heat at rest (e.g. using anticholinergic drugs such as antihistamines or TCAs), and patients with schizophrenia who are using anticholinergic or antiepileptic medications

Heat Exhaustion
- clinical features relate to loss of circulating volume caused by exposure to heat stress
- "water depletion": heat exhaustion occurs if lost fluid not adequately replaced
- "salt depletion": heat exhaustion occurs when losses replaced with hypotonic fluid
Heat Stroke
- life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
- divided into classical and exertional subtypes
- if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, other infections)

Table 24. Heat Exhaustion vs. Heat Stroke

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Classical Heat Stroke</th>
<th>Exertional Heat Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Occurs in setting of high ambient temperatures (e.g. heat wave, poor ventilation)</td>
<td>Occurs with high endogenous heat production (e.g. exercise) that overwhelms homeostatic mechanisms</td>
</tr>
<tr>
<td></td>
<td>Often patients are older, poor, or sedentary or immobile</td>
<td>Patients often younger, more active</td>
</tr>
<tr>
<td></td>
<td>Dry, hot skin</td>
<td>Skin often diaphoretic</td>
</tr>
<tr>
<td></td>
<td>Temp usually &gt; 104.9°F</td>
<td>Other features as for classical heat stroke, but may also have DIC, acute renal failure, rhabdomyolysis, marked lactic acidosis</td>
</tr>
<tr>
<td></td>
<td>May have elevated AST, ALT</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Rest in a cool environment</td>
<td>Cool body temperature with water mist (e.g. spray bottle) and standing fans</td>
</tr>
<tr>
<td></td>
<td>IV NS if orthostatic hypotension; otherwise replace losses slowly PO</td>
<td>Ice water immersion also effective; monitor body temperature closely to avoid hypothermic overshoot</td>
</tr>
<tr>
<td></td>
<td>Secure airway because of seizure and aspiration risk</td>
<td>Secure airway because of seizure and aspiration risk</td>
</tr>
<tr>
<td></td>
<td>Give fluid resuscitation if still hypotensive after above therapy</td>
<td>Give fluid resuscitation if still hypotensive after above therapy</td>
</tr>
<tr>
<td></td>
<td>Avoid α-agonists (e.g. epinephrine), peripheral vasoconstriction, and antipyretics (e.g. ASA)</td>
<td>Avoid α-agonists (e.g. epinephrine), peripheral vasoconstriction, and antipyretics (e.g. ASA)</td>
</tr>
</tbody>
</table>

Hypothermia and Cold Injuries

HYPOTHERMIA
- predisposing factors: extremes of age, lack of housing, drug overdose, EtOH ingestion, trauma (incapacitating), cold water immersion, outdoor sports
- treatment based on re-warming and supporting cardiorespiratory function
- complications: coagulopathy, acidosis, ventricular dysrhythmias (VFib), asystole, volume and electrolyte depletion
- labs: CBC, electrolytes, ABG, serum glucose, Cr/BUN, Mg²⁺, Ca²⁺, amylase, coagulation profile
- imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- monitors: ECG, rectal thermometer, Foley catheter, NG tube, monitor metabolic status frequently

Table 25. Classification of Hypothermia

<table>
<thead>
<tr>
<th>Class</th>
<th>Temp</th>
<th>Symptoms/Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>89.6 - 94.8°F</td>
<td>Tachypnea, tachycardia, ataxia, dysarthria, shivering</td>
</tr>
<tr>
<td>Moderate</td>
<td>82.4 - 88.4°F</td>
<td>Loss of shivering, dysrhythmias, Osborne (J) waves on ECG, decreased LOC, combative behavior, muscle rigidity, dilated pupils</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;82.4°F</td>
<td>Coma, hypotension, acidemia, VFib, asystole, flaccidity, apnea</td>
</tr>
</tbody>
</table>

Re-warming Options
- gentle fluid and electrolyte replacement in all (due to cold diuresis)
- Passive External Re-warming
  - suitable for most stable patients with core temperature >90°F
  - involves covering patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
- Active External Re-warming
  - involves use of warming blankets
  - beware of "afterdrop" phenomenon
  - safer when done in conjunction with active core re-warming
- Active Core Re-warming
  - generally for patients with core temperature <90°F, and/or with cardiovascular instability
  - avoids "afterdrop" seen with AER alone
  - re-warm core by using
    - warmed humidified oxygen, IV fluids
    - peritoneal dialysis with warm fluids
    - gastric/colonic/pleural irrigation with warm fluids
    - external circulation (cardiopulmonary bypass machine) is most effective and fastest

Afterdrop Phenomenon
Warming of extremities causes vasodilation and movement of cool pooled blood from extremities to core, resulting in a drop in core temperature leading to cardiac arrest
Approach to Cardiac Arrest in the Hypothermic Patient

- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 min; may have profound bradycardia
- if any pulse at all (even very slow) do NOT do CPR
  - if in VFib try to defibrillate up to maximum 3 shocks if core temperature <86°F
  - intubate if required, ventilate with warmed, humidified O₂
- medications (vasopressors, antidysrhythmics) may not be effective at low temperatures
  - controversial; may try one dose
- focus of treatment is re-warming

FROSTBITE

Classification

- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
  - 1st degree
    - symptoms: initial paresthesia, pruritus
    - signs: erythema, edema, hyperemia, no blisters
  - 2nd degree
    - symptoms: numbness
    - signs: blistering (clear), erythema, edema
  - 3rd degree
    - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
    - signs: hemorrhagic blisters, skin necrosis, edema, no movement

Management

- treat for hypothermia: O₂, IV fluids, maintenance of body warmth
- remove wet and constrictive clothing
- immerse in 104-107.6°F agitated water for 10-30 min (very painful; administer adequate analgesia)
- clean injured area and leave it open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin
- tetanus prophylaxis
- consider penicillin G as frost bite injury at high risk of infection
- surgical intervention may be required to release restrictive eschars
- never allow a thawed area to re-chill/freeze

Burns

- see Plastic Surgery, PL16

Physical Exam

- burn size
  - rule of nines; does not include 1st degree burns
- burn depth
  - superficial: epidermis only (e.g. sunburn)
  - partial thickness: into superficial dermis or hair follicles, sweat glands
  - full thickness: all layers of the skin
  - deep: involvement of fat, muscle, even bone

Management

- remove noxious agent/stop burning process
- establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury)
- resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)
- fluid boluses if unstable
  - Parkland Formula: Ringer’s lactate 4 cc/kg/% BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
- urine output is best measure of resuscitation, should be 40-50 cc/h or 0.5 cc/kg/h; avoid diuretics
- pain relief: continuous morphine infusion with breakthrough bolus
- investigations: CBC, electrolytes, U/A, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, systemic antibiotics infrequently indicated
- tetanus prophylaxis if burn is deeper than superficial dermis

Disposition

- admit
  - 2nd degree burns >10% BSA or any significant 3rd degree burns
  - 2nd degree burns on face, hands, feet, perineum, or across major joints
  - electrical, chemical burns, and inhalation injury
  - burn victims with underlying medical problems or immunosuppressed patients
Inhalation Injury

Etiology
- CO or cyanide poisoning
- direct thermal injury: limited to upper airway
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

History and Physical Exam
- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin (unreliable, usually post-mortem finding)
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO2 normal but O2 saturation low suggests CO poisoning

Investigations
- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± bronchoscopy

Management
- CO poisoning: 100% O2 ± hyperbaric O2 (controversial)
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators

Bites

MAMMALIAN BITES
- see Plastic Surgery, PL10

History
- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, rabies risks, HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, “fight bites”

Physical Exam
- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status

Investigations
- if bony injury or infection suspected, check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds ± CT to rule out cranial perforation

Initial Management
- wound cleansing and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
- culture wound if signs of infection (erythema, necrosis, or pus); obtain anaerobic cultures if wound foul smelling, necrotizing, or abscess; notify lab that sample is from bite wound

Prophylactic Antibiotics
- types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
- a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present (efficacy not proven)
- dog and cat bites (pathogens: Pasteurella multocida, S. aureus, S. viridans)
  - 80% of cat bites, 5% of dog bites become infected
  - 1st line: amoxicillin + clavulanic acid
- human bites (pathogens: Eikenella corrodens, S. aureus, S. viridans, oral anaerobes)
  - 1st line: amoxicillin + clavulanic acid
- rabies (see Infectious Diseases, ID21)
  - reservoirs: warm-blooded animals except rodents, lagomorphs (e.g. rabbits)
  - post-exposure vaccine is effective; treatment depends on local prevalence
- suturing
  - vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  - allow avascular structures (i.e. pretibial regions, hands, and feet) to heal by secondary intention
- tetanus immunization if >10 yr or incomplete primary series

Consider Admission if:
- Moderate to severe infections
- Infections in immunocompromised patients
- Not responding to oral therapy
- Penetrating injuries to tendons, joints, CNS
- Open fractures
SNAKE BITES
- history, physical exam, investigations, and initial management similar to mammalian bites
- additional management issues
  - snake bites are rarely fatal, but proper precautions must be taken
  - supportive management, observe for compartment syndrome, analgesia, tetanus prophylaxis
  - contact State Poison Information Center for consultation
  - for the Massasauga rattlesnake ONLY: if no signs of local tissue damage AND an INR is normal at 6 h after the bite, the patient may be discharged
  - there is NO evidence that constriction bands are helpful AND can be harmful
- if envenomation present, administer antivenom as directed by local Poison Information Center

INSECT BITES
- bee stings
  - 5 types of reactions to stings (local, large local, systemic, toxic, unusual)
  - history and physical exam key to diagnosis; no lab test will confirm
  - investigations: CBC, electrolytes, BUN, Cr, glucose, ABGs, ECG
  - ABC management, epinephrine 0.1 mg IV over 5 min if shock, antihistamines, cimetidine 300 mg IV/IM/PO, steroids, β-agonists for SOB/wheezing 3 mg in 5 mL NS via nebulizer, local site management
- West Nile virus (see Infectious Diseases, ID25)

Near Drowning
- most common in children <4 yr and teenagers
- causes lung damage, hypoxemia, and may lead to hypoxic encephalopathy
- must also assess for shock, C-spine injuries, hypothermia, and scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

Physical Exam
- ABCs, vitals: watch closely for hypotension
- lungs: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVS: murmurs, dysrhythmias, JVP (CHF, pneumothorax)
- H&N: assess for C-spine injuries
- neuro: GCS or AVPU, pupils, focal deficits

Investigations
- labs: CBC, electrolytes, ABGs, Cr, BUN, INR, PTT, U/A (drug screen, myoglobin)
- imaging: CXR (pulmonary edema, pneumothorax) ± C-spine imaging
- ECG

Management
- ABCs, treat for trauma, shock, hypothermia
- cardiac and O2 monitors, IV access
- intensive respiratory care
  - ventilator assistance if decreased respirations, pCO₂ >50 mmHg, or pO₂ <60 mmHg on maximum O₂
  - may require intubation for airway protection, ventilation, pulmonary toilet
  - high flow O₂/CPAP/BiPAP may be adequate but some may need mechanical ventilation with positive end-expiratory pressure
- dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, and acidosis
- vomiting: very common, NG suction to avoid aspiration
- convulsions: usually respond to O₂; if not, diazepam 5-10 mg IV slowly
- bronchospasm: bronchodilators
- bacterial pneumonia: not necessary to prophylax with antibiotics unless contaminated water or hot-tub (Pseudomonas)
- always initiate CPR in drowning-induced cardiac arrest even if patient hypothermic; continue CPR until patient is fully rewarmed

Disposition
- non-significant submersion: discharge after short observation
- significant submersion (even if asymptomatic): long period of observation (24 h) as pulmonary edema may appear late
- CNS symptoms or hypoxemia: admit
- severe hypoxemia, decreased LOC: ICU
Toxicology

“ABCD3EFG“ of Toxicology

- basic axiom of care is symptomatic and supportive treatment
- address underlying problem only once patient is stable
  
  A  Airway (consider stabilizing the C-spine)
  B  Breathing
  C  Circulation
  D1  Drugs
    * ACLS as necessary to resuscitate the patient
    * universal antidotes
  D2  Draw bloods
  D3  Decontamination (decrease absorption)
  E  Expose (look for specific toxidromes)/Examine the patient
  F  Full vitals, ECG monitor, Foley, X-rays
  G  Give specific antidotes and treatments

- go back and reassess
- call Poison Information Center
- obtain corroborative history from family, bystanders

D1 – Universal Antidotes

- treatments that will not harm patients and may be essential

Dextrose (glucose)
- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W
- children: 0.25 g/kg (2-4 mL/kg) IV of D25W

Oxygen
- do not deprive a hypoxic patient of oxygen no matter what the antecedent medical history (i.e. even COPD with CO2 retention)
- if depression of hypoxic drive, intubate and ventilate
- exception: paraquat or diquat (herbicides) inhalation or ingestion (oxygen radicals increase morbidity)

Naloxone (central µ-receptor competitive antagonist, shorter t1/2 than naltrexone)
- antidote for opioids: administration is both diagnostic and therapeutic (1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    * response to naloxone can be drastic, so stepwise delivery of initial 2 mg bolus is recommended
    * draw up 2 mg to deliver IV/IM/SL/SC or via ETT (ETT dose = 2-2.5x IV dose)
      - 1st dose 0.4 mg
      - if no response, deliver 2nd dose 0.6 mg
      - if still no response, deliver remaining 1 mg
  - child
    * 0.01 mg/kg initial bolus IV/IO/ETT
    * 0.1 mg/kg if no response and opioid still suspected to max of 10 mg
- maintenance dose
  - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
  - hourly infusion rate at 2/3 of initial dose that produced patient arousal

Thiamine (Vitamin B1)
- 100 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke's encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke's encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine unavailable
- must assume all undifferentiated comatose patients are at risk
D2 – Draw Bloods

- essential tests
  - CBC, electrolytes, BUN/Cr, glucose, INR/PTT, osmolality
  - ABGs, measure O₂ sat
  - ASA, acetaminophen, EtOH levels
- potentially useful tests
  - drug levels – this is NOT a serum drug screen
  - Ca²⁺, Mg²⁺, PO₄³⁻
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical presentation

Serum Drug Levels
- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only)

Table 26. Toxic Gaps (see Nephrology, NP14)

<table>
<thead>
<tr>
<th>Metabolic Acidosis</th>
<th>Increased POG: “MAE DIE” (if it ends in “-ol”, it will likely increase the POG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol*</td>
<td>Methanol</td>
</tr>
<tr>
<td>Uremia</td>
<td>Acetone</td>
</tr>
<tr>
<td>Diabetic ketoacidosis/Starvation ketoacidosis</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Phenformin*/Paraldehyde*</td>
<td>Diuretics (glycerol, mannitol, sorbitol)</td>
</tr>
<tr>
<td>Lactate (anything that causes seizures or shock)</td>
<td>Isopropanol</td>
</tr>
<tr>
<td>Ethylene glycol*</td>
<td>Ethylene glycol</td>
</tr>
<tr>
<td>Salicylates*</td>
<td></td>
</tr>
<tr>
<td>Cyanide, CO*</td>
<td></td>
</tr>
<tr>
<td>Alcoholic ketoacidosis</td>
<td></td>
</tr>
<tr>
<td>Toluene, theophylline*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased AG</th>
<th>Increased O₂ saturation gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrolyte imbalance (increased Na⁺/K⁺/Mg²⁺)</td>
<td>Carboxyhemoglobin</td>
</tr>
<tr>
<td>Hypoalbuminemia (50% fall in albumin – 5.5 mEg/L decrease in the AG)</td>
<td>Methemoglobin</td>
</tr>
<tr>
<td>Lithium, bromine elevation</td>
<td>Sulfmethemoglobin</td>
</tr>
<tr>
<td>Paraproteins (multiple myeloma)</td>
<td>Note: normal POG does not rule out toxic alcohol; only an elevated gap is helpful</td>
</tr>
</tbody>
</table>

Normal AG
- High K⁺: pyelonephritis, obstructive nephropathy, renal tubular acidosis IV, TPN
- Low K⁺: small bowel losses, acetazolamide, renal tubular acidosis I, II

Table 27. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
<th>Selected Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Hypoventilation (↑ pCO₂)</td>
<td>CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, EtOH)</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation (↓ pCO₂)</td>
<td>Salicylates, CO, other asphyxiants</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>↑ AG metabolic acidosis</td>
<td>“MUDPILES CAT”: see Table 26</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>Digitalis glycosides, fluoride, potassium</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hypoglycemia</td>
<td>Oral hypoglycemic agents, insulin, EtOH, ASA</td>
</tr>
<tr>
<td>Osmolality and Osmolar Gap</td>
<td>Elevated osmolar gap</td>
<td>“MAE DIE”: see Table 26</td>
</tr>
<tr>
<td>ECG</td>
<td>Wide QRS complex</td>
<td>TCA,s, quinidine, other class la and lc antidysrhythmic agents</td>
</tr>
<tr>
<td></td>
<td>Prolonged QT interval</td>
<td>Terfenadine, astemizole, antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Atrioventricular block</td>
<td>Ca²⁺ antagonists, digitalis glycosides, phenytoinpropanolamine</td>
</tr>
<tr>
<td>Abdominal X-Ray</td>
<td>Radiopaque pills or objects</td>
<td>“CHICES”: Calcium, Chloral hydrate, CO₂, Heavy metals, Iron, Potassium, Enteral coated Salicylates, and some foreign bodies</td>
</tr>
<tr>
<td>Serum Acetaminophen</td>
<td>Elevated level (&gt;140 mg/L or 1,000 µmol/L 4 h after ingestion)</td>
<td>May be only sign of acetaminophen poisoning</td>
</tr>
</tbody>
</table>
D3 – Decontamination and Enhanced Elimination

Ocular Decontamination
- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

Dermal Decontamination (wear protective gear)
- remove clothing, brush off toxic agents, irrigate all external surfaces

Gastrointestinal Decontamination
- single dose activated charcoal
  - adsorption of drug/toxin to AC prevents availability
  - contraindications: caustics, small bowel obstruction, perforation
  - dose: 10 g/g drug ingested or 1g/kg body weight
  - odorless, tasteless, prepared as slurry with H2O
- whole bowel irrigation
  - 500 mL/h (child) to 2,000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
  - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated
  - indications
    - awake, alert, can be nursed upright OR intubated and airway protected
    - delayed release product
    - drug/toxin not bound to charcoal
    - drug packages (if any evidence of breakage → emergency surgery)
  - contraindications
    - evidence of ileus, perforation, or obstruction
  - surgical removal in extreme cases
    - indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
- no evidence for the routine use of cathartics (i.e. ipecac)

Urine Alkalization
- may be used for: ASA, methotrexate, phenobarbital, chlorpropamide
- weakly acidic substances can be trapped in alkali urine (pH >7.5) to increase elimination

Multidose Activated Charcoal
- may be used for: carbamazepine, phenobarbital, quinine, theophylline
- for toxins which undergo enterohepatic recirculation
- removes drug that has already been absorbed by drawing it back into GI tract
- various regimens: 12.5 g (1/4 bottle) PO q1h or 25 g (1/2 bottle) PO q2h until non-toxic

Hemodialysis
- indications/criteria for hemodialysis
  - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution, or rapid plasma equilibration
  - removal of toxin will cause clinical improvement
  - advantage is shown over other modes of therapy
  - predicted that drug or metabolite will have toxic effects
  - impairment of normal routes of elimination (cardiac, renal, or hepatic)
  - clinical deterioration despite maximal medical support
- useful for the following toxins
  - methanol
  - lithium
  - ethylene glycol
  - phenobarbital
  - salicylates
  - chloral hydrate (→ trichloroethanol)
  - others include theophylline, carbamazepine, valproate, methotrexate

E – Expose and Examine the Patient
- vital signs (including temperature), skin (needle tracks, color), mucous membranes, pupils, odors, and CNS
- head-to-toe survey including
  - C-spine
  - signs of trauma, seizures (incontinence, “tongue biting”, etc.), infection (meningismus), or chronic alcohol/drug abuse (track marks, nasal septum erosion)
- mental status

Position Paper Update: Ipecac Syrup for Gastrointestinal Decontamination
Clin Toxicol 2013;51:134-139
Study: Systematic review of 12 new studies (2003-2011) and summary of older studies (animal studies, volunteer studies, case reports).
Conclusions: There is debate in the literature as to whether or not the use of ipecac should be completely abandoned, or whether it may remain useful in certain special circumstances. Concerns regarding the use of ipecac include the variability of its effects depending on elapsed time of administration and its interference with other treatments such as activated charcoal. Furthermore, ipecac use has a number of side effects, such as diarrhea, drowsiness, and prolonged vomiting, as well as some rare side effects which may contribute to death. Despite these, ipecac has a high margin of safety. While routine administration of ipecac is not appropriate, it may be beneficial in certain circumstances. For example, its use may be considered when there is a substantial risk of serious toxicity, there are no contraindications (such as high risk of aspiration), no alternative treatment option exists (or when the administration of ipecac will have no effect on the alternative treatment option), and there can be timely delivery of ipecac (<90 min).
### Table 28. Specific Toxidromes

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Overdose Signs and Symptoms</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>Hyperthermia</td>
<td>Antidepressants (e.g. TCAs)</td>
</tr>
<tr>
<td></td>
<td>Dilated pupils</td>
<td>Ciclobenzaprine (Flexeril®)</td>
</tr>
<tr>
<td></td>
<td>&quot;Hot as a hare&quot;</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>&quot;Blind as a bat&quot;</td>
<td>Antihistamines (e.g. diphenhydramine)</td>
</tr>
<tr>
<td></td>
<td>Dry skin</td>
<td>Antiparkinsonians</td>
</tr>
<tr>
<td></td>
<td>&quot;Dry as a bone&quot;</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Vasodilation</td>
<td>Antispasmodics</td>
</tr>
<tr>
<td></td>
<td>&quot;Ried as a beet&quot;</td>
<td>Belladonna alkaloids (e.g. atropine)</td>
</tr>
<tr>
<td></td>
<td>Agitation/hallucinations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&quot;Mad as a hatter&quot;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ileus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lost their tone and the heart goes on alone&quot;</td>
<td></td>
</tr>
<tr>
<td>Cholinergic</td>
<td>&quot;DUMBELS&quot;</td>
<td>Natural plants: mushrooms, trumpet flower</td>
</tr>
<tr>
<td></td>
<td>Diaphoresis, Diarrhea, Decreased BP</td>
<td>Anticholinesterases: physoxiogmine</td>
</tr>
<tr>
<td></td>
<td>Urination</td>
<td>Insecticides (organophosphates, carbamates)</td>
</tr>
<tr>
<td></td>
<td>Miosis</td>
<td>Nerve gases</td>
</tr>
<tr>
<td></td>
<td>Bronchospsam, Bronchorhea, Bradycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Emesis, Excitation of skeletal muscle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Salivation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal</td>
<td>Dysphoria, dysphagia</td>
<td>Major tranquillizers</td>
</tr>
<tr>
<td></td>
<td>Rigidty and tremor</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Motor restlessness, crawling sensation (akathisia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant movements (dyskinesia)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dystonia (muscle spasms, laryngospasm, trismus, oculoogic crisis, torticollis)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Derangements</td>
<td>Increased respiratory rate</td>
<td>CO poisoning (carboxyhemoglobin)</td>
</tr>
<tr>
<td></td>
<td>Decreased LOC</td>
<td>Drug ingestion (methemoglobin, sulfmethemoglobin)</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyanosis unresponsive to O₂</td>
<td></td>
</tr>
<tr>
<td>Opioid, Sedative/</td>
<td>Hypothermia</td>
<td>EtOH</td>
</tr>
<tr>
<td>Hypnotic, EtOH</td>
<td>Hypotension</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td>Opioids (morphine, heroin, fentanyl, etc.)</td>
</tr>
<tr>
<td></td>
<td>Dilated or constricted pupils (pinpoint in opioid)</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td>CNS depression</td>
<td>Gamma hydroxybutyrate</td>
</tr>
<tr>
<td>Sympathomimetic</td>
<td>Increased temperature</td>
<td>Amphetamines, caffeine, cocaine, LSD, phencyclidine</td>
</tr>
<tr>
<td></td>
<td>CNS excitation (including seizures)</td>
<td>Ephedrine and other decongestants</td>
</tr>
<tr>
<td></td>
<td>Tachycardia, HTN</td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>N/V</td>
<td>Sedative or EtOH withdrawal</td>
</tr>
<tr>
<td></td>
<td>Diaphoresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilated pupils</td>
<td></td>
</tr>
<tr>
<td>Serotonin Syndrome</td>
<td>Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, hyperthermia, diarrea, HTN</td>
<td>MAOI, TCA, SSRI, opiate analgesics</td>
</tr>
</tbody>
</table>

**Note:** ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

### F – Full Vitals, ECG Monitor, Foley, X-Rays

### G – Give Specific Antidotes and Treatments

**Urine Alkalization Treatment for ASA Overdose**
- urine pH > 7.5
- fluid resuscitate first, then 3 amps NaHCO₃/L of D5W @ 1.5 x maintenance
- add 20-40 mEq/L KCl if patient is able to urinate

**Table 29. Protocol for Warfarin Overdose**

<table>
<thead>
<tr>
<th>INR</th>
<th>Management: Consider Prothrombin Complex Concentrate (Octaplex®, Beriplex®) for any elevated INR, AND either life-threatening bleeding, or a plan for the patient to undergo a surgical procedure within the next 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5.0</td>
<td>Cessation of warfarin administration, observation, serial INR/PT</td>
</tr>
<tr>
<td>5.1–9.0</td>
<td>If no risk factors for bleeding, hold warfarin x 1-2 d and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding</td>
</tr>
<tr>
<td>9.1–20.0</td>
<td>Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary</td>
</tr>
<tr>
<td>&gt; 20.0</td>
<td>Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4h) if needed</td>
</tr>
</tbody>
</table>
Table 30. Specific Antidotes and Treatments for Common Toxins*

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Decontaminate (activated charcoal) N-acetylcysteine</td>
<td>Often clinically silent; evidence of liver/renal damage delayed &gt;24 h Toxic dose &gt;200 mg/kg (&gt;7.5 g adult) Monitor drug level 4 h post-ingestion; also liver enzymes, INR, PTT, BUN, Cr Hypoglycemia, metabolic acidosis, encephalopathy → poor prognosis</td>
</tr>
<tr>
<td>Acute Dystonic Reaction</td>
<td>Benztropine: 1-2 mg IM/IV then 2 mg PO x 3 d OR Diphenhydramine 1-2 mg/kg IV, then 25 mg PO qid x 3 d</td>
<td>Benztropine (Cogentin®) has euphoric effect and potential for abuse</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Decontaminate (activated charcoal) Supportive care</td>
<td>Special antidotes available; consult Poison Information Center</td>
</tr>
<tr>
<td>ASA</td>
<td>Decontaminate (activated charcoal) Alkalize urine; want urine pH &gt;7.5</td>
<td>Monitor serum pH and drug levels closely Monitor K⁺ level; may require supplement for urine alkalization Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or end-organ damage (i.e. unable to diurese)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Decontaminate (activated charcoal) Flumazenil Supportive care</td>
<td>Consult Poison Information Center</td>
</tr>
<tr>
<td>β-blockers</td>
<td>Decontaminate (activated charcoal) Consider high dose insulin euglycemia therapy Some dialyzable, some use intralipids</td>
<td>Consult Poison Information Center</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Decontaminate (activated charcoal) CaCl₂ 1-4 g of 10% solution IV if hypotensive Other: high dose insulin euglycemia, inotropes or intralipids</td>
<td>Order ECG, electrolytes (especially Ca²⁺, Mg²⁺, Na⁺, K⁺)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Decontaminate (activated charcoal) if oral Aggressive supportive care</td>
<td>β-blockers are contraindicated in acute cocaine toxicity Intralipid for life-threatening symptoms</td>
</tr>
<tr>
<td>CO Poisoning</td>
<td>See Inhalation Injury, ER46 Supportive care 100% O₂</td>
<td></td>
</tr>
<tr>
<td>Cyanide</td>
<td>Hydroxocobalamin</td>
<td>Use for life-threatening dysrhythmias unresponsive to conventional therapy, 6 h serum digoxin &gt;9.4 mg/mL, initial K⁺ &gt;5 mEq/L, ingestion &gt;10 mg (adult)/&gt;4 mg (child) Common dysrhythmias includeVFib, VTach, and conduction blocks</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Decontaminate (activated charcoal) Digoxin-specific Ab fragments 10-20 vials IV if acute; 3-4 if chronic 1 vial (40 mg) neutralizes 0.5 mg of toxin</td>
<td>Use for life-threatening dysrhythmias unresponsive to conventional therapy, 6 h serum digoxin &gt;9.4 mg/mL, initial K⁺ &gt;5 mEq/L, ingestion &gt;10 mg (adult)/&gt;4 mg (child) Common dysrhythmias includeVFib, VTach, and conduction blocks</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Thiamine 100 mg IM/IV Manage airway and circulatory support</td>
<td>Hypoglycemia very common in children Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH Order serum EtOH level and glucose level; treat glucose level appropriately</td>
</tr>
<tr>
<td>Ethylene Glycol/ Methanol</td>
<td>Fomepizole (4-methylpyrazole) 15 mg/kg IV load over 30 min, then 10 mg/kg q12h OR Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h</td>
<td>CBC, electrolytes, glucose, ethanol level Consider hemodialysis</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate 25-50 mg IV</td>
<td>For unfractionated heparin overdose only</td>
</tr>
<tr>
<td>Insulin IM/SC/ Oral Hypoglycemic</td>
<td>Glucose IV/PQ/NG tube Glucagon: 1-2 mg IM (if no access to glucose)</td>
<td>Glyburide carries highest risk of hypoglycemia among oral agents Consider octreotide for oral hypoglycemics (50-100 µg SC q6h) in these cases; consult local Poison Information Center</td>
</tr>
<tr>
<td>MDMA</td>
<td>Decontaminate (activated charcoal), supportive care</td>
<td>Monitor CK; treat rhabdomyolysis with high flow fluids: aggressive external cooling for hyperthermia</td>
</tr>
<tr>
<td>Opioids</td>
<td>See Universal Antidotes, ER48</td>
<td></td>
</tr>
<tr>
<td>TCAs</td>
<td>Decontaminate (activated charcoal) Aggressive supportive care NaHCO₃ bolus for wide QRS/seizures</td>
<td>Flumazenil antidote contraindicated in combined TCA and benzodiazepine overdose Also consider cardiac and hypertension support, seizure control Intralipid therapy (consult local Poison Information Center)</td>
</tr>
</tbody>
</table>

*Call local Poison Information Center for specific doses and treatment recommendations
Alcohol Related Emergencies

- see Psychiatry, PS18

Acute Intoxication
- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia → may progress to coma
- hypotension (peripheral vasodilation)
- if obtunded, rule out
  - head trauma/intracranial hemorrhage
  - associated depressants/street drugs, toxic alcohols
  - may also contribute to respiratory/cardiac depression
  - hypoglycemia (screen with bedside glucometer)
  - hepatic encephalopathy: confusion, altered LOC, coma
  - precipitating factors: GI bleed, infection, sedation, electrolyte abnormalities, protein meal
  - Wernicke's encephalopathy (ataxia, ophthalmoplegia, delirium)
  - post-ictal state, basilar stroke

Withdrawal
- beware of withdrawal signs
- treatment
  - diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1h until calm
  - frequency of dosing may have to be increased depending on clinical response
  - may use CIWA protocol and give benzodiazepines as above until CIWA < 10
  - thiamine 100 mg IM/IV then 50-100 mg/d
  - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  - admit patients with DT or multiple seizures

Table 31. Alcohol Withdrawal Signs

<table>
<thead>
<tr>
<th>Time Since Last Drink</th>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8 h</td>
<td>Mild withdrawal</td>
<td>Generalized tremor, anxiety, agitation, but no delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autonomic hyperactivity (sinus tachycardia, insomnia, N/V)</td>
</tr>
<tr>
<td>1-2 d</td>
<td>Alcoholic hallucinations</td>
<td>Visual (most common), auditory, and tactile hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitals often normal</td>
</tr>
<tr>
<td>8 h-2 d</td>
<td>Withdrawal seizures</td>
<td>Typically brief generalized tonic-clonic seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May have several within a few hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT head if focal seizures have occurred</td>
</tr>
<tr>
<td>3-5 d</td>
<td>DT</td>
<td>5% of untreated withdrawal patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severely confused state, fluctuating LOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitation, insomnia, hallucinations/delusions, tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia, hyperpyrexia, diaphoresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High mortality rate</td>
</tr>
</tbody>
</table>

Cardiovascular Complications
- HTN
- cardiomyopathy: SOB, edema
- dysrhythmias (“holiday heart”)
  - AFib (most common), atrial flutter, SVT, VTach (especially Torsades if hypomagnesemic/ hypokalemic)

Metabolic Abnormalities
- alcoholic ketoacidosis
  - AG metabolic acidosis, urine ketones, low glucose, and normal osmolality
  - history of chronic alcohol intake with abrupt decrease/cessation
  - malnourished, abdominal pain with N/V
  - treatment: dextrose, thiamine (100 mg IM/IV prior to dextrose), volume repletion (with NS)
  - generally resolves in 12-24 h
- other alcohols
  - ethylene glycol → CNS, CVS, renal findings
  - methanol
    - early: lethargy, confusion
    - late: headache, visual changes, N/V, abdominal pain, tachypnea
  - both ethylene glycol and methanol produce severe metabolic acidosis with anion gap (as the alcohol is metabolized) and osmolar gap (initially after ingestion but before metabolism)
  - EtOH co-ingestion is protective
  - treatment
    - urgent hemodialysis required
    - fomepizole 15 mg/kg IV bolus OR EtOH 10% IV bolus and infusion to achieve blood level of 100 mg/dL (EtOH loading may be done PO)
• consider folic acid for methanol, and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites
• other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

Gastrointestinal Abnormalities
• gastritis
  • common cause of abdominal pain and GI bleed in chronic alcohol users
• pancreatitis
  • serum amylase very unreliable in patients with chronic pancreatitis, may need serum lipase
  • hemorrhagic form (15%) associated with increased mortality
  • fluid resuscitation very important
• hepatitis
  • AST/ALT ratio >2 suggests alcohol as the cause as well as elevated GGT with acute ingestion
• peritonitis/spontaneous bacterial peritonitis
  • leukocytosis, fever, generalized abdominal pain/tenderness
  • occasionally accompanies cirrhosis
  • paracentesis for diagnosis (common pathogens: E. coli, Klebsiella, Streptococcus)
• GI bleeds
  • most commonly gastritis or ulcers, even if patient known to have varices
  • consider Mallory-Weiss tear secondary to retching
  • often complicated by underlying coagulopathies
  • minor: treat with antacids
  • severe or recurrent: endoscopy

Disposition
• before patient leaves ED ensure stable vital signs, can walk unassisted, fully oriented
• offer social services to find shelter or detox program
• ensure patient can obtain any medications prescribed and can complete any necessary follow-up

Approach to the Overdose Patient

History
• age, weight, underlying medical problems, medications
• substance and how much
• time and symptoms since exposure determines prognosis and need for decontamination
• route
• intention, suicidality

Physical Exam
• focus on: ABCs, LOC/GCS, vitals, pupils

Disposition from the Emergency Department
• methanol, ethylene glycol
  • delayed onset, admit and watch clinical and biochemical markers
• TCAs
  • prolonged/delayed cardiotoxicity warrants admission to monitored (ICU) bed
  • if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  • sinus tachycardia alone (most common finding) with history of OD warrants observation in ED
• hydrocarbons/smoke inhalation
  • pneumonitis may lag 6-8 h
  • consider observation for repeated clinical and radiographic examination
• ASA, acetaminophen
  • if borderline level, get second level 2-4 h after first
  • for ASA, must have at least 2 levels going down before discharge (3 levels minimum)
• oral hypoglycemics
  • admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  • observe asymptomatic patient for at least 8 h

Psychiatric Consultation
• once patient medically cleared, arrange psychiatric intervention if required
• beware – suicidal ideation may not be expressed
Psychiatric Emergencies

Approach to Common Psychiatric Presentations

• see Psychiatry, PS2
• before seeing patient, ensure your own safety; have security/police available if necessary

History
• safety
  ▪ assess suicidality: suicidal ideation (SI), intent, plan, lethal means, and past attempts
  ▪ assess homicidality: homicidal ideation (HI), access to weapons, intended victim, and history of violence
  ▪ driving and children
  ▪ command hallucinations
• identify current stressors and coping strategies
• mood symptoms: manic, depressive
• anxiety: panic attacks, generalized anxiety, phobias, obsessive-compulsive disorder, post-traumatic stress disorder
• psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, negative symptoms (affective flattening, alogia, avolition)
• substance use history: most recent use, amount, previous withdrawal reactions
• past psychiatric history, medications, adherence with medications
• medical history: obtain collateral if available

Physical Exam
• complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder
• mental status exam: general appearance, behavior, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability

Investigations
• investigations vary with age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
• as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum Cr, BUN, osmolality
• blood levels of psychiatric medications
• CT head if suspect neurological etiology
• LP if indicated

Acute Psychosis

Differential Diagnosis
• primary psychotic disorder (e.g. schizophrenia)
• secondary to medical condition (e.g. delirium)
• drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
• infectious (CNS)
• metabolic (hypoglycemic, hepatic, renal, thyroid)
• structural (hemorrhage, neoplasm)

Management
• violence prevention
  ▪ remain calm, empathic, and reassuring
  ▪ ensure safety of staff and patients, have extra staff and/or security on hand
  ▪ patients demonstrating escalating agitation or overt violent behavior may require physical restraint and/or chemical tranquilization
• treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
  ▪ benzodiazepines: lorazepam 2 mg PO/IM/SL
  ▪ antipsychotics: olanzapine 5 mg PO, haloperidol 5 mg PO/IM
• treat underlying medical condition
• psychiatry or Crisis Intervention Team consult
**Suicidal Patient**

**Epidemiology**
- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr

**Management**
- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), previous attempts
- admit if there is evidence of intent and organized plan, access to lethal means, psychiatric disorder, intoxication (suicidal ideation may resolve with few days of abstinence)
- patient may require certification if unwilling to stay voluntarily
- do not start long-term medications in the ED
- psychiatry or Crisis Intervention Team consult

**Common Pediatric ED Presentations**

**Modified Glasgow Coma Score**

<table>
<thead>
<tr>
<th>Modified GCS for Infants</th>
<th>Eye Opening</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Opening</td>
<td>4 – spontaneously</td>
<td>5 – coos, babbles</td>
<td>6 – normal, spontaneous movement</td>
</tr>
<tr>
<td></td>
<td>3 – to speech</td>
<td>4 – irritable cry</td>
<td>5 – withdraws to touch</td>
</tr>
<tr>
<td></td>
<td>2 – to pain</td>
<td>3 – cries to pain</td>
<td>4 – withdraws to pain</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
<td>2 – moans to pain</td>
<td>3 – decorticate flexion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 – no response</td>
<td>2 – decerebrate extension</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified GCS for Children &lt;4 yr</th>
<th>Eye Opening</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Opening</td>
<td>4 – spontaneously</td>
<td>5 – oriented, social, speaks, interacts</td>
<td>6 – normal, spontaneous movement</td>
</tr>
<tr>
<td></td>
<td>3 – to speech</td>
<td>4 – confused speech, disoriented, consolable</td>
<td>5 – localizes to pain</td>
</tr>
<tr>
<td></td>
<td>2 – to pain</td>
<td>3 – inappropriate words, not consolable/aware</td>
<td>4 – withdraws to pain</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
<td>2 – incomprehensible, agitated, restless, not aware</td>
<td>3 – decorticate flexion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 – no response</td>
<td>2 – decerebrate extension</td>
</tr>
</tbody>
</table>

**Respiratory Distress**

- see *Pediatrics*, P89

**History and Physical Exam**
- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
  - see *Pediatrics*, P3 for age specific vital signs
- pulse paradoxus
- wheezing, grunting, vomiting

### Table 33. Stridorus Upper Airway Diseases: Diagnosis

<table>
<thead>
<tr>
<th>Feature</th>
<th>Group</th>
<th>Bacterial Tracheitis</th>
<th>Epiglottitis¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age Range (yr)</td>
<td>0.5-4</td>
<td>5-10</td>
<td>2-8</td>
</tr>
<tr>
<td>Prodrome</td>
<td>Days</td>
<td>Hours to days</td>
<td>Minutes to hours</td>
</tr>
<tr>
<td>Temperature</td>
<td>Low grade</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Radiography</td>
<td>Steeple sign</td>
<td>Exudates in trachea</td>
<td>Thumb sign</td>
</tr>
<tr>
<td>Etiology</td>
<td>Parainfluenza</td>
<td>S. aureus/GAS</td>
<td>H. Influenzae type b</td>
</tr>
<tr>
<td>Barley Cough</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Dripping</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Appear Toxic</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intubation/ICU</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>NOTE</td>
<td>Oral exam</td>
<td>Oral exam</td>
<td>No oral exam, consult ENT</td>
</tr>
</tbody>
</table>

¹Now rare with Hib vaccine in common use

**Any trauma or suspected trauma patient <1 yr of age with a large, boggy scalp hematoma requires U/S or CT

**High Risk Patients**

<table>
<thead>
<tr>
<th>SAD PERSONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex = male</td>
</tr>
<tr>
<td>Age &gt; 45 yr old</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Previous attempts</td>
</tr>
<tr>
<td>Ethanol use</td>
</tr>
<tr>
<td>Rational thinking loss</td>
</tr>
<tr>
<td>Suicide in family</td>
</tr>
<tr>
<td>Organized plan</td>
</tr>
<tr>
<td>No spouse, no support system</td>
</tr>
<tr>
<td>Serious illness</td>
</tr>
</tbody>
</table>

**In Pediatric Respiratory Distress, Must also Rule Out:**
- Anaphylaxis
- Foreign body
- Pneumonia
- Bronchiolitis
Management
- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - humidified O₂ should not be given (no evidence for efficacy)
  - racemic epinephrine q1h x 3 doses, observe for 'rebound effects'
  - nebulized 1:1000 epi (racemic has limited availability)
  - dexamethasone x 1 dose
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy
- bacterial tracheitis
  - start croup therapy, but may have poor response
  - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g., cloxacillin), pending C&S
  - epiglottitis
    - 4 D's: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
    - do not examine oropharynx or agitate patient
    - immediate anesthesia, ENT call – intubate
    - then IV fluids, antibiotics, blood cultures
- asthma
  - supplemental O₂ if saturation <90% or PaO₂ <60%
  - bronchodilator therapy: salbutamol (Ventolin®) 0.15 mg/kg by masks q20min x 3
  - add 250–500 µg ipratropium (Atrovent®) to first 3 doses salbutamol
  - give corticosteroid therapy as soon as possible after arrival (prednisolone 2 mg/kg, dexamethasone 0.3 mg/kg)
  - if critically ill, not responding to inhaled bronchodilators or steroids: give IV bolus, then infusion of MgSO₄
  - IV β₂-agonists if critically ill and not responding to above

Febrile Infant and Febrile Seizures

FEBRILE INFANT
- see Pediatrics, P54
- for fever >100.4°F without obvious focus
  - <28 d
    - admit
    - full septic workup (CBC and differential, blood C&S, urine C&S, LP ± stool C&S, CXR if indicated)
    - treat empirically with broad spectrum IV antibiotics
  - 28-90 d
    - as above unless infant meets Rochester criteria (see sidebar), investigate as indicated by history and physical
  - >90 d
    - toxic: admit, treat, full septic workup
    - non-toxic and no focus: investigate as indicated by history and physical

FEBRILE SEIZURES
- see Pediatrics, P86

Etiology
- children aged 6 mo to 6 yr with fever or history of recent fever
- typical vs. atypical febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- relatively well looking after seizure

Investigations and Management
- if it is a febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
- note: may also have fever but may not meet criteria for febrile seizure
- ± EEG (especially if first seizure), head U/S (if fontanelle open)

Table 34. Typical vs. Atypical Febrile Seizures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>&lt;15 min</td>
<td>&gt;15 min</td>
</tr>
<tr>
<td>Type of Seizure</td>
<td>Generalized</td>
<td>Focal features</td>
</tr>
<tr>
<td>Frequency</td>
<td>1 in 24 h</td>
<td>&gt;1 in 24 h</td>
</tr>
</tbody>
</table>
**Abdominal Pain**

- see [Pediatrics, P39](#)

**History**

- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake

**Physical Exam**

- HEENT, respiratory, abdominal exam including DRE, testicular/genital exam

**Table 35. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents**

<table>
<thead>
<tr>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colic</td>
<td>Malrotation with volvulus</td>
</tr>
<tr>
<td>UTI</td>
<td>Hirschsprung’s disease</td>
</tr>
<tr>
<td>Constipation</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Incarcerated hemia</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Duodenal atresia</td>
</tr>
<tr>
<td>IBD</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Strep throat</td>
<td>Testicular torsion</td>
</tr>
<tr>
<td>Sickle cell disease crisis</td>
<td>Ecstic pregnancy</td>
</tr>
<tr>
<td>DKA</td>
<td>Trauma</td>
</tr>
<tr>
<td>Functional</td>
<td>Pyloric stenosis</td>
</tr>
</tbody>
</table>

*Remember to keep an index of suspicion for child abuse*

**Common Infections**

- see [Pediatrics, P54](#)

**Table 36. Antibiotic Treatment of Pediatric Bacterial Infections**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MENINGITIS SEPSIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal</td>
<td>GBS, E. coli, Listeria, Gram-negative bacilli</td>
<td>ampicillin + cefotaxime</td>
</tr>
<tr>
<td>1-3 mo</td>
<td>Same pathogens as above and below</td>
<td>ampicillin + cefotaxime + vancomycin</td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td>S. pneumoniae, H. influenzae type b (&gt;5 yr), meningococcus</td>
<td>ceftriaxone + vancomycin</td>
</tr>
<tr>
<td><strong>OTITIS MEDIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st line</td>
<td>S. pneumoniae, H. influenzae type b, M. catarrhalis</td>
<td>amoxicillin 80-90 mg/kg per day</td>
</tr>
<tr>
<td>2nd line</td>
<td>clarithromycin 15 mg/kg/d bid (for penicillin allergy)</td>
<td></td>
</tr>
<tr>
<td>Treatment failure</td>
<td>90 mg/kg/d amoxicillin and 6.4 mg/kg/d clavulanate divided into bid dosage</td>
<td></td>
</tr>
<tr>
<td><strong>STREP PHARYNGITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group A β-hemolytic Streptococcus</td>
<td>penicillin/amoxicillin or erythromycin (penicillin allergy)</td>
</tr>
<tr>
<td><strong>UTI</strong></td>
<td>E. coli, Proteus, H. influenzae, Pseudomonas, S. saprophyticus, Enterococcus, GBS</td>
<td>Oral: cephalxin (older children) IV: ampicillin and aminoglycoside</td>
</tr>
<tr>
<td><strong>PNEUMONIA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 mo</td>
<td>Viral, S. pneumoniae, C. trachomatis, B. pertussis, S. aureus, H. influenzae</td>
<td>cefuroxime ± macrolide (erythromycin) OR ampicillin ± macrolide</td>
</tr>
<tr>
<td>3 mo-5 yr</td>
<td>Viral, S. pneumoniae, S. aureus, H. influenzae, Mycoplasma pneumoniae</td>
<td>ampicillin/amoxicillin or cefuroxime</td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>As above</td>
<td>ampicillin/amoxicillin + macrolide or cefuroxime + macrolide</td>
</tr>
</tbody>
</table>
Child Abuse and Neglect

- see *Pediatrics*, P14
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - HI: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken Baby Syndrome: diffuse brain injury, subdural/SAH, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures age <1 yr, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - GU/GI injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STD/pregnancy, recurrent vomiting or diarrhea

Common Medications

Table 37. Commonly Used Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>325-650 mg PO q4-6h pm</td>
<td>Pain control</td>
<td>Max 4 g daily</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>30-100 g PO in 250 mL H₂O</td>
<td>Poisoning/overdose</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>325-650 mg PO q4h max 4g/d stroke/MI risk, 81-325 mg PO OD 160 mg chewed</td>
<td>Pain control Cardiac prevention ACS</td>
<td></td>
</tr>
<tr>
<td>β-blockers (metoprolol)</td>
<td>5 mg slow IV q5min x 3 if no contraindications</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>anxiety: 2-10 mg PO tid/qid alcohol withdrawal: 10-20 mg PO/IV q1h titrated to signs/symptoms</td>
<td>Anxiety Alcohol withdrawal</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg SC bid</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>anaphylaxis: 0.1-0.5 mg IM; can repeat q10-15min</td>
<td>Anaphylaxis Max 1 mg/dose</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5-1.0 µg/kg IV</td>
<td>Procedural sedation</td>
<td>Very short acting narcotic (complication=apnea)</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>0.3 mg IV bolus q5min x 3 doses</td>
<td>Reversal of procedural sedation</td>
<td>Benzodiazepine antagonist Can cause seizures/status epilepticus in chronic benzodiazepine users</td>
</tr>
<tr>
<td>Furosemide (Lasix)</td>
<td>CHF: 40-80 mg IV HTN: 10-40 mg PO bid</td>
<td>Monitor for electrolyte imbalances</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>0.5-1.0 g/kg (1-2 mL/kg) IV of D50W</td>
<td>Hypoglycemia/DKA</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2.5-5.0 mg PO/IM initial effective dose 6-20 mg/d</td>
<td>Psychosis Monitor with Parkinson’s; results in CNS depression</td>
<td></td>
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<tr>
<td>Ibuprofen</td>
<td>200-800 mg PO tid pm max 1,200 mg/d</td>
<td>Mild to moderate acute pain Analgesic and anti-inflammatory properties</td>
<td></td>
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<tr>
<td>Insulin</td>
<td>bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per h</td>
<td>Hyperglycemia Explain levels before admission</td>
<td></td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>2-3 puffs inhaled tid-qid, max 12 puffs/d</td>
<td>Asthma Contraindicated with peanut/soy allergy Caution with narrow-angle glaucoma</td>
<td></td>
</tr>
<tr>
<td>Lidocaine with epi</td>
<td>max 7 mg/kg SC</td>
<td>Local anesthetic Not to be used in fingers, nose, toes, penis, ears</td>
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<tr>
<td>Lidocaine w/o epi</td>
<td>max 5 mg/kg SC</td>
<td>Local anesthetic</td>
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<tr>
<td>Lorazepam</td>
<td>anxiety: 0.5-2 mg PO/IM/IV q6-8h status epilepticus: 4 mg IV repeat up to q5min</td>
<td>Anxiety Status epilepticus</td>
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<tr>
<td>Midazolam</td>
<td>50 µg/kg IV</td>
<td>Procedural sedation</td>
<td>Short acting benzodiazepine (complication=apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation</td>
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Table 37. Commonly Used Medications (continued)

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<th>Drug</th>
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<th>Indications</th>
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<tr>
<td>Morphine</td>
<td>15-30 mg PO q8-12h, 0.1-0.2 mg/kg max 15 mg IV q4h</td>
<td>Mild to moderate acute/chronic pain, prescribed in combination with NSAIDs or acetaminophen</td>
<td>GI and constipation side effects, do not crush, cut, or chew</td>
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<tr>
<td>Naloxone</td>
<td>0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ET(2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg</td>
<td>Comatose patient, opioid overdose, reversal in procedural sedation</td>
<td></td>
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<tr>
<td>Nitroglycerin</td>
<td>acute angina: 0.3-0.6 mg SL q3-5min, OR 5 µg/min IV increasing by 5-20 µg/min q3-5min</td>
<td>Angina, Acute MI</td>
<td>Not to be used with other anti-hypertensives, not in right ventricular MI</td>
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<tr>
<td>Pericocet 10/325®</td>
<td>1-2 tabs PO q6h pm</td>
<td>Moderate pain control</td>
<td>Oxycodeone + acetaminophen Max 4 g acetaminophen daily</td>
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<tr>
<td>Phenytoin</td>
<td>Status epilepticus: see Table 14, ER26</td>
<td>Status epilepticus</td>
<td>Begin maintenance dose 12 h after loading dose, continuous ECG, BP monitoring mandatory</td>
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<tr>
<td>Polysporin®</td>
<td>Apply to affected area bid-tid</td>
<td>Superficial infections</td>
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<tr>
<td>Propofol</td>
<td>0.25-1 mg/kg IV</td>
<td>Procedural sedation</td>
<td>Short acting, anesthetic/sedative (complication = apnea, decreased BP)</td>
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<tr>
<td>Salbutamol</td>
<td>2 puffs inhaled q4-6h (4 yr) max 12 puffs/d</td>
<td>Asthma</td>
<td>Caution with cardiac abnormalities</td>
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<tr>
<td>Thiamine</td>
<td>100 mg IV/IM initially, then 50-100 mg IM/N/PO OD x 3d</td>
<td>To treat/prevent Wernicke’s encephalopathy</td>
<td>Caution in pregnancy</td>
</tr>
<tr>
<td>Tylenol #3®</td>
<td>1-2 tabs PO q4-6h pm</td>
<td>Pain control</td>
<td>Max 4 g acetaminophen daily</td>
</tr>
</tbody>
</table>

References

Polysporin® Apply to affected area bid-tid. Superficial infections.
Propofol 0.25-1 mg/kg IV. Procedural sedation. Short acting anesthetic/sedative (complication = apnea, decreased BP).
Salbutamol 2 puffs inhaled q4-6h (4 yr) max 12 puffs/d. Asthma. Caution with cardiac abnormalities.
Thiamine 100 mg IV/IM initially, then 50-100 mg IM/N/PO OD x 3d. To treat/prevent Wernicke’s encephalopathy. Caution in pregnancy.
Tylenol #3® 1-2 tabs PO q4-6h pm. Pain control. Max 4 g acetaminophen daily.
# Endocrinology

Liana Kaufman, Heather Sawula, and Derek Smith, chapter editors
Amanda Huynh, Jessica Huynh, and Vahagn Karapetyan, associate editors
Tina Hu, EBM editor
Dr. Julia Lowe, Dr. Adam C. Millar, and Dr. Phillip Segal, staff editors

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Acronyms

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<td>very low density lipoprotein</td>
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Basic Anatomy Review

Major Endocrine Organs

**HYPOTHALAMUS**
- Corticotropin-RH (CRH)
- Gonadotropin-RH (GnRH)
- Thyrotropin-RH (TSH)
- Growth hormone-RH (GHRH)
- Antidiuretic hormone (ADH)*
- Oxytocin*

**THYROID GLAND**
- Triiodothyronine (T3)
- Thyroxine (T4)

**ADRENAL GLAND**
- Cortex
  - Aldosterone
  - Cortisol
  - Androgens
  - Medulla
  - Catecholamines

**PARATHYROID GLANDS**
- Parathyroid hormone (PTH)

**TESTES**
- Testosterone

**PITUITARY GLAND**
- Anterior pituitary
  - Growth hormone (GH)
  - Prolactin (PRL)
  - Thyroid-stimulating hormone (TSH)
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH)
- Posterior pituitary
  - Antidiuretic hormone (ADH)*
  - Oxytocin*

**PARATHYROID GLANDS**
- Parathyroid hormone (PTH)

**PANCREAS**
- Insulin
- Glucagon
- Estrogen
- Progestosterone

**OVARIYES**
- Estrogen
- Progestosterone

**GENERAL FUNCTION OF ORGANS**

The Hypothalamic-Pituitary Axis
Information about cortical inputs, automatic function, environmental cues (light, temperature) and peripheral hormonal feedback is synthesized at the coordinating center of the endocrine system, the hypothalamus. The hypothalamus then sends signals to the pituitary to release hormones that affect the thyroid, adrenals, gonads, growth, milk production, and water balance.

**Anatomy ↔ Function**

Hypothalamic hormones: small peptides, non-binding protein → rapid degradation
- High [] in pituitary-portal blood system
- Low [ ] in peripheral circulation

Proximity of axis preserves the pulsatile output signals from the hypothalamic neurons.

**Thyroid**
Thyroid hormone is critical to 1) brain and somatic development in fetus and infants, 2) metabolic activity in adults, and 3) function of virtually every organ system.

**Adrenal**
Each gland, 6-8 g, has 1) a cortex with 3 layers that act like independent organs ( zona glomerulosa → aldosterone, fasciculata → cortisol, reticularis → androgen and estrogen precursors), and 2) a medulla that acts like a sympathetic ganglion to store/synthesize adrenaline and noradrenaline.

**Gonads**
Bifunctional: sex steroid synthesis and gamete production.

Sex steroids control sexuality and affect metabolic and brain functions.

**Parathyroid**
Synthesize and secrete PTH, a principle regulator of ECF Ca^2+ regulated by [Ca^2+]_i, Mg^2+ and 1,25(OH)2D (active metabolite of vit D), and phosphate.

**Pancreas**
Endocrine islet β-cells produce insulin: oppose glucose production (glycogenolysis, gluconeogenesis), increase glucose uptake into muscle and fat. Glucagon, epinephrine, cortisol, and GH are counterregulatory.

**Dyslipidemias**

**Definition**
- Metabolic disorders characterized by elevations of fasting plasma LDL-cholesterol, and/or triglycerides (TG), and/or low HDL-cholesterol

**Overview of Lipid Transport**
- Lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apoproteins, and phospholipids
- Lipoproteins transport lipids within the body
- Apolipoproteins serve as enzyme co-factors, promote clearance of the particle by interacting with cellular receptors, and stabilize the lipoprotein micelle

**Figure 1. Endocrine system**

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Table 1. Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Apolipoproteins</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exogenous Pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylomicron</td>
<td>B-48, C, E, A-I, A-II, A-IV</td>
<td>• Transports dietary TG from gut to adipose tissue and muscle</td>
</tr>
<tr>
<td><strong>Endogenous Pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>B-100, C, E</td>
<td>• Transports hepatic synthesized TG from liver to adipose tissue and muscle</td>
</tr>
<tr>
<td>IDL</td>
<td>B-100, E</td>
<td>• Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core • Enriched in cholesterol esters</td>
</tr>
<tr>
<td>LDL</td>
<td>B-100</td>
<td>• Formed by further removal of residual TG from IDL core by hepatic lipase resulting in greater enriched particles with cholesterol esters • Transports cholesterol from liver to peripheral tissues (gonads, adrenals)</td>
</tr>
<tr>
<td>HDL</td>
<td>A-I, A-II, C, E</td>
<td>• Transports cholesterol from peripheral tissues to liver • Acts as a reservoir for apolipoproteins</td>
</tr>
</tbody>
</table>

Figure 2. Exogenous and endogenous biosynthetic lipid pathways

**Hypercholesterolemia**

**Table 2. Primary Hypercholesterolemias**

<table>
<thead>
<tr>
<th>Hypercholesterolemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>• 1/500 in U.S. population with high penetrance • Autosomal codominant Canadian population • More prevalent in French Canadian population • Defect in the normal LDL receptor on cell membranes</td>
<td>↑ LDL ↑ TC</td>
<td>• Tendinous xanthomatosis (Achilles, patellar, and extensor tendons of hand) • Arcus cornealis • Xanthelasma • Heterozygotes: premature CAD, 50% risk of MI in men by age 30 • Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (&lt;20 yr) if untreated</td>
<td>• Homozygotes: improvement of LDL with HMG-CoA reductase inhibitors, often in combination with niacin, ezetimibe, or bile acid sequestrants • Homozygotes: partial control with portacaval shunt or LDL apheresis in conjunction with niacin; large dose atorvastatin is modestly effective</td>
</tr>
</tbody>
</table>

| Polygenic Hypercholesterolemia | • Few mild inherited defects in cholesterol metabolism | ↑ TC ↑ LDL | • Asymptomatic until vascular disease develops • No xanthomata | • HMG-CoA reductase inhibitors, ezetimibe, niacin, bile acid sequestrant |
SECONDARY HYPERCHOLESTEROLEMIA

**Etiology**
- endocrine: hypothyroidism
- renal: nephrotic syndrome
- immunologic: monoclonal gammopathy
- hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)
- nutritional: diet, anorexia nervosa
- drugs: cyclosporin, anabolic steroids, carbamazepine

Hypertriglyceridemia (Elevated Triglycerides)

### PRIMARY HYPERTRIGLYCERIDEMIA

**Table 3. Primary Hypertriglyceridemias**

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Lipoprotein Lipase Deficiency</td>
<td>Autosomal recessive deficiency of lipoprotein lipase or its cofactor</td>
<td>↑ TG Chylomicrons Moderate ↑ in VLDL</td>
<td>Hepatosplenomegaly</td>
<td>Decrease dietary fat intake to &lt;10% of total calories</td>
</tr>
<tr>
<td>Familial Hypertriglyceridemia</td>
<td>Several genetic defects resulting in ↑ hepatic VLDL synthesis or ↓ removal of VLDL</td>
<td>↑ TG ↑ VLDL</td>
<td>Possible premature CAD</td>
<td>Decrease dietary simple carbohydrates and fat intake</td>
</tr>
</tbody>
</table>

### SECONDARY HYPERTRIGLYCERIDEMIA

**Etiology**
- endocrine: obesity/metabolic syndrome, hypothyroidism (more for high LDL, not TG), acromegaly, Cushing’s syndrome, DM
- renal: chronic renal failure, polyclonal and monoclonal hypergammaglobulinemia
- hepatic: chronic liver disease, hepatitis, glycogen storage disease
- drugs: alcohol, corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
- other: pregnancy

Combined Hyperlipidemia

**Table 4. Primary Combined Hyperlipidemias**

<table>
<thead>
<tr>
<th>Hyperlipidemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Combined Hyperlipidemia</td>
<td>Over-population of VLDL and associated ↑ LDL 2↑ to excess hepatic synthesis of apolipoprotein B</td>
<td>↑ TC + TG ↑ VLDL ↑ LDL</td>
<td>Xanthelasma &amp; CAD and other vascular disease</td>
<td>Weight reduction</td>
</tr>
<tr>
<td>Dysbetalipoproteinemia</td>
<td>Abnormal apolipoprotein E</td>
<td>↑ TC + TG ↑ VLDL ↑ IDL</td>
<td>Tubercous, eruptive, palmar xanthomata</td>
<td>Weight reduction</td>
</tr>
</tbody>
</table>

Dyslipidemia and the Risk for Coronary Artery Disease

- increased LDL is a major risk factor for atherosclerosis and CAD as LDL is the major atherogenic lipid particle
- increased HDL is associated with decreased cardiovascular disease and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3-9 mmol/L) is an independent risk factor for CAD, especially in people with DM and in post-menopausal women
- treatment of hypertriglyceridemia has not been shown to reduce CAD risk
Screening
• screen men over age 40, women over age 50, or post-menopausal
• if following risk factors present, screen at any age
  ▫ DM
  ▫ cigarette smoking
  ▫ HTN (sBP >140, dBP >90)
  ▫ obesity
  ▫ family history of premature CAD
  ▫ clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
  ▫ evidence of atherosclerosis
  ▫ rheumatoid arthritis, SLE, psoriasis
  ▫ HIV infection on highly active antiretroviral therapy (HAART)
  ▫ chronic kidney disease (estimated GFR <60 mL/min/1.73 m²)
  ▫ erectile dysfunction
• screen children with a family history of hypercholesterolemia or chylomicronemia

Factors Affecting Risk Assessment
• metabolic syndrome
• apolipoprotein B (apo B)
  ▫ each atherogenic particle (VLDL, IDL, LDL, and lipoprotein A) contains one molecule of apo B
  ▫ serum [apo B] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome
• C-reactive protein (hs-CRP) levels
  ▫ highly sensitive acute phase reactant
  ▫ may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment

Treatment of Dyslipidemias

Approach to Treatment
For clinical guidelines see National Institutes of Health; Adult Treatment Panel III https://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf
• determine lipoprotein levels – obtain complete profile after 9 to 12 h fast
• identify presence of of clinical atherosclerotic disease that confers high risk for CHD events
• If 2+ risk factors (other than LDL) are present without CHD or CHD risk equivalent estimate 10 yr risk of CAD using Framingham model
• establish treatment targets according to level of risk

Table 5. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC)
and Drug Therapy in Different Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL Level at which to Initiate Therapeutic Lifestyle Changes (TLC)</th>
<th>LDL Level at which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD Risk Equivalents (10 yr risk &gt;20%)</td>
<td>&lt;10 mg/dL</td>
<td>≥100 mg/dL</td>
<td>130 mg/dL (100-129 mg/dL: drug optional)</td>
</tr>
<tr>
<td></td>
<td>≥130 mg/dL</td>
<td>10 yr risk 10-20%</td>
<td>≥130 mg/dL</td>
</tr>
<tr>
<td></td>
<td>≥160 mg/dL</td>
<td>0 yr risk &lt;10%</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>0-1 Risk Factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>

Table 6. Treatment of Hypercholesterolemia and Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Treatment of Hypercholesterolemia</th>
<th>Treatment of Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Conservative: 4-6 mo trial unless high risk group, in which case medical treatment should start immediately</td>
<td></td>
</tr>
<tr>
<td>• Diet</td>
<td></td>
</tr>
<tr>
<td>• Decrease fat: &lt;30% calories</td>
<td></td>
</tr>
<tr>
<td>• Decrease saturated fat: &lt;10% calories</td>
<td></td>
</tr>
<tr>
<td>• Decrease cholesterol: &lt;200 mg/d</td>
<td></td>
</tr>
<tr>
<td>• Increase fiber: &gt;30 g/d</td>
<td></td>
</tr>
<tr>
<td>• Decrease alcohol intake to ≤1-2 drinks/d</td>
<td></td>
</tr>
<tr>
<td>• Smoking cessation</td>
<td></td>
</tr>
<tr>
<td>• Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</td>
<td></td>
</tr>
<tr>
<td>• Weight loss: target BMI &lt;25</td>
<td></td>
</tr>
<tr>
<td>• Medical</td>
<td></td>
</tr>
<tr>
<td>• HMG-CoA reductase inhibitors, ezetimibe, bile acid sequestrants, niacin (see Common Medications, E53)</td>
<td></td>
</tr>
<tr>
<td>• Conservative: 4-6 mo trial</td>
<td></td>
</tr>
<tr>
<td>• Diet</td>
<td></td>
</tr>
<tr>
<td>• Decrease fat and simple carbohydrates</td>
<td></td>
</tr>
<tr>
<td>• Increase omega-3 polyunsaturated fatty acid</td>
<td></td>
</tr>
<tr>
<td>• Control blood sugars</td>
<td></td>
</tr>
<tr>
<td>• Decrease alcohol intake to ≤1-2 drinks/d</td>
<td></td>
</tr>
<tr>
<td>• Smoking cessation</td>
<td></td>
</tr>
<tr>
<td>• Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</td>
<td></td>
</tr>
<tr>
<td>• Weight loss: target BMI &lt;25</td>
<td></td>
</tr>
<tr>
<td>• Medical: fibrates, niacin (see Common Medications, E53)</td>
<td></td>
</tr>
<tr>
<td>• Indications:</td>
<td></td>
</tr>
<tr>
<td>• Failed conservative measures</td>
<td></td>
</tr>
<tr>
<td>• TG &gt;10 mmol/L (805 mg/dL) to prevent pancreatitis</td>
<td></td>
</tr>
<tr>
<td>• Combined hyperlipidemia</td>
<td></td>
</tr>
</tbody>
</table>

Treatment Effect
Each 40 mg/dL (1.0 mmol/L) decrease in LDL corresponds to 20–25% relative risk reduction in cardiovascular disease

For Statin Follow-Up
• Liver enzymes and lipid profile: liver enzymes measured at the beginning of treatment then once after therapy initiated; lipids (once stabilized) measured annually; order both if patient complains of jaundice, RUQ pain, dark urine
• CK at baseline and if patient complains of myalgia
• D/C statin if CK >10x upper limit of normal or patient has persistent myalgia

Intensive Lipid Lowering in CAD: TNT
NEJM 2005;352:1425-1435
Study: Multicenter, randomized, double-blinded trial with median follow-up of 4.9 yr.
Patients: 10,001 patients with CAD and LDL-C <3.4 mmol/L (<131.5 mg/dL)
Intervention: 80 mg vs. 10 mg atorvastatin daily.
Main Outcomes: Death from CAD, MI, cardiac arrest, or stroke.
Results: A primary event occurred in 8.7% of the patients receiving intensive therapy, compared to 10.5% of patients receiving standard therapy (HR 0.78, p<0.001). There was no difference in overall mortality. Incidence of persistent transaminase elevations was higher in the intensive therapy group (1.2% vs. 0.2%, p<0.001).
Conclusion: Intensive statin therapy is associated with lower rates of CAD events than standard therapy, but also a higher rate of transaminase elevation.

Simvastatin to Lower CAD Risk – The Heart Protection Study (HPS)
Lancet 2002;360:7-22
Study: Randomized, double-blind, placebo-controlled trial with median follow-up of 5.9 yr.
Patients: 20,536 patients with coronary disease, other occlusive arterial disease or diabetes (aged 40-80 yr) who had a total cholesterol level of ≥3.5 mmol/L
Intervention: Simvastatin 40 mg/d or placebo.
Main Outcomes: Mortality, fatal or non-fatal vascular events.
Results: The use of simvastatin significantly decreased total mortality (12.9 vs. 14.7, p=0.0003) and the first event rate of any cardiovascular event by 25% (p<0.001).
Conclusion: Treatment with simvastatin improved survival and cardiovascular outcomes in high-risk CAD patients.
Overview of Glucose Regulation

Pre-Diabetes (Impaired Glucose Tolerance/Impaired Fasting Glucose)

- 1-5% per yr go on to develop DM
- 50-80% revert to normal glucose tolerance
- weight loss may improve glucose tolerance
- increased risk of developing macrovascular complications
- lifestyle modifications decrease progression to DM by 58%

Diagnostic Criteria
- impaired fasting glucose (IFG): fasting blood glucose (FBG) 110-125 mg/dL (6.1-6.9 mmol/L)
- impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 140-200 mg/dL (7.8-11.0 mmol/L)

Diabetes Mellitus

Definition
- syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/relative deficiency of insulin, or a reduction in biological effectiveness of insulin, or both

Diagnostic Criteria
- any one of the following is diagnostic
  - presence of classic symptoms of DM (polyuria, polydipsia, polyphagia, weight loss, blurry vision, nocturia, ketonuria) PLUS random blood glucose (BG) ≥ 200 mg/dL (11.1 mmol/L)
  - on at least two separate occasions
    - FPG ≥ 126 mg/dL (7.0 mmol/L) (fasting = no caloric intake for at least 8 h) OR
    - 2 h 75 g OGTT ≥200 mg/dL (11.1 mmol/L) OR
    - random PG ≥200 mg/dL (11.1 mmol/L) OR
    - HbA1c ≥6.5%

Glucose Related Emergencies
- DKA
- HHS
- Hypoglycemia
Etiology and Pathophysiology

Table 7. Etiologic Classification of Diabetes Mellitus

| I. Type 1 DM (immune-mediated β cell destruction, usually leading to absolute insulin deficiency) |
| II. Type 2 DM (ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance 2nd to β cell dysfunction) |
| III. Other specific causes of DM: |
| a. Genetic defects of β cell function (e.g., MODY – Maturity-Onset Diabetes of the Young) or insulin action |
| b. Diseases of the exocrine pancreas: |
| • Pancreatitis, pancreactectomy, neoplasia, cystic fibrosis, hemochromatosis ("bronze diabetes") |
| c. Endocrinopathies: |
| • Acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, hyperthyroidism |
| d. Drug-induced: |
| • Glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, clozapine |
| e. Infections: |
| • Congenital rubella, CMV, coxsackie |
| f. Genetic syndromes associated with DM: |
| • Down’s syndrome, Klinefelter’s syndrome, Turner’s syndrome |

IV. Gestational Diabetes Mellitus (see Obstetrics, OB13)

Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Onset</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usually &lt;30 yr of age</td>
<td>Usually &gt;40 yr of age</td>
<td></td>
</tr>
<tr>
<td>Increasing incidence in pediatric population 2nd to obesity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Epidemiology

| More common in Caucasians |
| Less common in Asians, Hispanics, Aboriginals, and Blacks |
| Accounts for 5-10% of all DM |

Etiology

| Autoimmune |
| Complex and multifactorial |

Genetics

| Monozygotic twin concordance is 30-40% |
| Associated with HLA class II DR3 and DR4, with either allele present in up to 95% of type 1 DM |
| Certain DQ alleles also confer a risk |

Pathophysiology

| Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion |
| Autoimmune process is believed to be triggered by environmental factors (e.g., viruses, bovine milk protein, urea compounds) |
| Pancreatic cells are infiltrated with lymphocytes resulting in islet cell destruction |
| 80% of β cell mass is destroyed before features of DM present |

Natural History

- After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin
- Once these cells are destroyed, there is complete insulin deficiency

Circulating Autoantibodies

| Islet cell Ab present in up to 60-85% |
| Most common islet cell Ab is against glutamic acid decarboxylase (GAD) |
| Up to 60% have Ab against insulin |

<10%

Blood Glucose Control in Type 2 DM – UKPDS 33

Lancet 1998;352:837-853

Study: Randomized controlled trial (mean follow-up 10 yr).

Patients: 3,867 patients with newly diagnosed type 2 DM (mean age 53 yr, 61% men, 81% white, mean fasting plasma glucose [FPG] 6.1-15.0 mmol/L (<236 mg/dL) – 236 mg/dL) without hyperglycemic symptoms.

Exclusions included severe cardiovascular disease, renal disease, retinopathy, and others.

Intervention: Intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L (<222 mg/dL)) vs. conventional treatment with diet alone (target FPG <7 mmol/L (<126 mg/dL)).

Main Outcomes: DM-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia), DM-related death, and all-cause mortality.

Results: Patients allocated to intensive treatment had lower median HbA1c levels (p<0.001).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RRR (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM-related endpoint</td>
<td>12 (0.029)</td>
</tr>
<tr>
<td>DM-related death</td>
<td>10 (0.34)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6 (0.44)</td>
</tr>
</tbody>
</table>

Patients allocated to intensive therapy had less hypoglycemic episodes and greater weight gain.

Conclusion: Intensive blood glucose control reduces microvascular, but not macrovascular complications in type 2 DM.
Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus (continued)

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Personal history of other autoimmune diseases including Graves’, myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia</td>
<td>• Age &gt;40 yr</td>
<td>• Schizophrenia</td>
</tr>
<tr>
<td>• Abdominal obesity/overweight</td>
<td>• First-degree relative with DM</td>
<td>• Fatty liver</td>
</tr>
<tr>
<td>• Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander)</td>
<td>• HTN</td>
<td>• Hyperuricemia</td>
</tr>
<tr>
<td>• Hx of IGT or IFG</td>
<td>• Diabetes</td>
<td></td>
</tr>
<tr>
<td>• HDL</td>
<td>• PCOS</td>
<td></td>
</tr>
<tr>
<td>• Hx of gestational DM or macroscopic baby</td>
<td>• Gestational DM</td>
<td></td>
</tr>
</tbody>
</table>

Body Habitus

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Normal to thin</td>
<td>• Typically overweight with increased central obesity</td>
</tr>
</tbody>
</table>

Acute Complication

<table>
<thead>
<tr>
<th>Screening</th>
<th>Diabetic ketoacidosis (DKA) in severe cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Subclinical prodrôme can be detected in first and second-degree relatives of those with type 1 DM by the presence of pancreatic islet autoantibodies</td>
<td>• Hypersomolar hyperglycemic state (HHS) in severe cases</td>
</tr>
</tbody>
</table>

Glycemic Targets

- HbA1c reflects glycemic control over 3 mo and is a measure of patient’s long-term DM control.
- Therapy in most individuals with type 1 or type 2 DM should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications.
- More intensive glucose control, HbA1c <6.5%, may be targeted in patients with a shorter duration of DM with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia.
- Less stringent HbA1c targets (7.1-8.5%) may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to attain HbA1c <7.0% despite treatment intensification.
- There may be harm associated with strategy to target HbA1c <6.0% in certain patients with type 2 DM (see ACCORD trial, E9).

Diet

- Daily carbohydrate intake 45-60% of energy, protein 15-20% of energy, and fat <35% of energy.
- Intake of saturated fats <7% and polyunsaturated fats <10% of total calories each.
- Limit sodium, alcohol, and caffeine intake.
- Type 1: Carbohydrate counting is used to titrate insulin regimen.
- Type 2: Weight reduction.

Lifestyle

- Regular physical exercise to improve insulin sensitivity, lower lipid concentrations and control blood pressure.
- Smoking cessation.

Medical Treatment: Oral Antihyperglycemic Agents and/or Incretin Therapy (Type 2 DM)

- Initiate oral antihyperglycemic therapy and/or incretin therapy within 2-3 mo if lifestyle management does not result in glycemic control.
- If HbA1c >8.5%, initiate pharmacologic therapy immediately and consider combination oral therapy or insulin immediately.
- See Common Medications, E52 for details on antihyperglycemic agents.

Medical Treatment: Insulin (Figure 5)

- Used for type 1 DM at onset, may be used in type 2 DM at any point in treatment.
- Routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only).
- Bolus insulins: short-acting (Insulin regular), rapid-acting analogue (Insulin aspart, Insulin lispro, Insulin glulisine).
- Basal insulins: intermediate-acting (Insulin NPH), long-acting analogue (Insulin detemir, Insulin glargine).

Treatment of Diabetes

American Diabetes Association (ADA) 2014 Guidelines

<table>
<thead>
<tr>
<th>Target</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>&lt; 7.0%</td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>≤70-130 mg/dL</td>
</tr>
<tr>
<td>Pre-prandial glucose</td>
<td>≤110 mg/dL</td>
</tr>
<tr>
<td>2h post-prandial glucose</td>
<td>≤180 mg/dL</td>
</tr>
<tr>
<td>Lipids</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≤140/80 mmHg</td>
</tr>
</tbody>
</table>

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 DM: the Look AHEAD Trial (2013;365:193-200)

- Study: RCT with 8.6 yr of median follow-up.
- Population: 5,145 overweight or obese patients with type 2 DM.
- Intervention: Intensive lifestyle intervention promoting weight loss through decreased caloric intake and increased physical activity (intervention) or diabetes support and education (control).
- Primary Outcome: First occurrence of death from cardiovascular (CV) causes, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for angina.
- Results: There was no significant difference between intensive and conventional glycemic control for all-cause mortality or cardiovascular mortality. Targeting intensive glycemic control reduced the risk of any coronary event, the composite risk of microvascular disease, nephropathy, retinal photocoagulation, and nephropathy. The risks of both mild and severe hypoglycemia were increased with targeting intensive glycemic control.
- Conclusions: Intensive glycemic control did not reduce all-cause mortality and cardiovascular mortality compared to conventional glycemic control. Intensive glycemic control reduced the risk of microvascular complications while increasing the risk of hypoglycemia. Intensive glycemic control may also reduce the risk of non-fatal MI in trials exclusively dealing with glycemic control in usual care settings.
Adapted from: 2008;32(suppl1):S56

E9 Endocrinology Disorders of Glucose Metabolism

• premixed insulins (% Humulin R and % NPH) 30/70; premixed insulin analogues (Biphasic Insulin aspart, Insulin lispro/lispro protamine)
• estimated total daily insulin requirement: 0.5–0.7 units/kg (often start with 0.3–0.5 units/kg/day)

| Initial Drug | Metformin
|--------------|--------------------------------------------------|
| Efficacy (HbA1c) | High
| Side effects (Costs) | Low Risk | Neutral/Loss | GL/Lactic Acidosis | Low |

**Healthy eating, weight control, increased activity**

| Two-Drug Combinations | Metformin + Sulfonylurea
|------------------------|--------------------------------------------------|
| Efficacy (HbA1c) | High
| Weight | Moderate risk
| Cost | Gain |
| Side effects | Hypoglycemia | Edema, HF, Fx’s |

**After ~3 months: if needed to reach individualized HbA1c target, proceed to two-drug combination (order not meant to denote any specific preference)**

| Three-Drug Combinations | Metformin + DPP-4 Inhibitor
|------------------------|--------------------------------------------------|
| Efficacy (HbA1c) | High
| Weight | Intermediate
| Cost | Low risk
| Side effects | GI |

**After ~3-6 months: if combination therapy that includes basal insulin fails to achieve HbA1c. Proceed to complex insulin strategy, usually in combination with one or two noninsulin agents:**

**Table 9. Available Insulin Formulations**

<table>
<thead>
<tr>
<th>Insulin Type (trade name)</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting insulin analogues</strong>&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin aspart (NovoRapid&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3.5 h</td>
</tr>
<tr>
<td>Insulin lispro (Humalog&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>10-15 min</td>
<td>1-2 h</td>
<td>3.5-4.75 h</td>
</tr>
<tr>
<td>Insulin glulisine (Apidra&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3.5 h</td>
</tr>
</tbody>
</table>

**Short-acting insulins**<sup>2</sup><sup>3</sup>

| Insulin R<sup>®</sup> | 30 min | 2-3 h | 6.5 h |
| Novolin Toronto<sup>®</sup>

**Basal Insulins**

| Intermediate-acting | Insulin | 1-3 h | 5-8 h | Up to 18 h |

| Long-acting basal insulin analogues | Insulin detemir (Levemir<sup>®</sup>) | 90 min | Not applicable | Up to 24 h (glargine 24 h, detemir 16-24 h) |

| Insulin glargine (Lantus<sup>®</sup>) |

**Pre-Mixed Insulins**

- Premixed regular insulin – NPH
- Humulin 30/70®
- Novolin 30/70®

- Premixed insulins analogues
  - Biphasic insulin aspart (NovoMix 30®)
  - Insulin lispro/lispro protamine (Humalog Mix25® and Mix50®)

---

**Figure 4. Approach to treatment of hyperglycemia in type 2 DM**
Adapted from: Can J Diabetes 2006;30(suppl1):S56

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</tr>
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</tr>
</tbody>
</table>

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  - Biphasic insulin aspart (NovoMix 30®)
  - Insulin lispro/lispro protamine (Humalog Mix25® and Mix50®)

---

**Effects of Intensive Glucose Lowering in Type 2 DM: The ACCORD Trial**
NEJM 2010;362:1563-1574

**Study:** Multicenter RCT.

**Patients:** 10,251 patients (mean age 62.2) with type 2 DM, and cardiovascular risk factors.

**Intervention:** Intensive therapy targeting a HbA1c level of less than 6.0% or standard therapy targeting 7.0 to 7.9%.

**Outcomes:** First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.

**Results:** The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV mortality, nonfatal MI, and CHF in the intensive therapy group. There were increased rates of all hyperglycemic events, any nonhemodynamic serious adverse events, fluid retention, and weight gain >10 kg, but lower systolic and diastolic blood pressure in the intensive therapy group. There was an increased incidence of elevated ALT (1–3 times upper limit) and ACE drug use in the standard therapy group.

**Conclusions:** Intensive glucose lowering therapy in type 2 DM does not improve clinic outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy.

Additional research is required to discern the cause.

---

**Effects of Intensive Blood Pressure Control in Type 2 DM: The ACCORD Trial**
NEJM 2010;362:1575-1585

**Study:** RCT, unblinded with 4.7 yr of mean follow-up.

**Population:** 4,733 patients with type 2 DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (SBP) between 130-180 mmHg.

**Intervention:** DBP control less than 120 mmHg (intensive) or 140 mmHg (standard).

**Primary Outcomes:** Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death).

**Results:** Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI 3.3-4.5) vs. 2.1 (95% CI 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.3% vs. 1.27%, p<0.001); especially bradycardia or arrhythmia (0.5% vs. 0.1%, p<0.002) and hyperkalemia (0.4% vs. 0.04%, p=0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.22%/yr vs. 0.53%/yr, p<0.001) and nonfatal stroke incidence (0.30%/yr vs. 0.47%/yr, p=0.03) in the intensive therapy arm.

**Conclusions:** Intensive BP lowering to less than 120 mmHg vs. 140 mmHg in patients with type 2 DM and CV risk factors does not reduce major CV event risk reduction except for stroke events.

---

**Effects of Combination Lipid Therapy in Type 2 DM: The ACCORD Trial**
NEJM 2010;362:1583-1594

**Study:** RCT, double-blinded trial with 4.7 yr of mean follow-up.

**Population:** 5,518 patients with type 2 DM.

**Intervention:** Statin with or without fibrate therapy.

**Primary Outcome:** Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death).

**Results:** No significant differences in primary outcome between the two arms. No difference in all MI, all stroke, or all-cause mortality by study arms.

**Conclusions:** The addition of fibrate therapy to statin therapy in patients with type 2 DM does not reduce major CV event risk.
Insulin Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 DM</td>
<td>Oral hypoglycemic agent + basal insulin</td>
</tr>
<tr>
<td></td>
<td>• Start with 10 units at bedtime of basal insulin</td>
</tr>
<tr>
<td></td>
<td>• Titrate up by 1 unit until FBG &lt; 7.0 mmol/L (126 mg/dL)</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>Multiple daily injections (MDI)</td>
</tr>
<tr>
<td></td>
<td>• Estimated total insulin requirement is 0.5-0.7 U/kg</td>
</tr>
<tr>
<td></td>
<td>• 40% is given as basal insulin at bedtime</td>
</tr>
<tr>
<td></td>
<td>• 20% is given as bolus insulin before breakfast, lunch, and dinner</td>
</tr>
<tr>
<td></td>
<td>• Continue metformin but discontinue secretagogue</td>
</tr>
<tr>
<td>Split-mixed</td>
<td>Estimated total insulin requirement is 0.5-0.7 U/kg</td>
</tr>
<tr>
<td></td>
<td>• 2/3 dose is given as pre-mixed insulin before breakfast</td>
</tr>
<tr>
<td></td>
<td>• 1/3 dose is given as pre-mixed insulin before dinner</td>
</tr>
<tr>
<td></td>
<td>• Continue metformin but discontinue secretagogue</td>
</tr>
</tbody>
</table>

Table 10. Insulin Regimens for Type 2 DM and Type 1 DM

Variable Insulin Dose Schedule (“Sliding/Supplemental/Correction Scale”)

- for patients on Basal-Bolus MDI regimen: patient takes usual doses of basal insulin but varies doses of bolus insulin based on BG reading at time of dose
- use baseline bolus insulin dose when within BG target range; add or subtract units when above or below target
- when used in hospital (including perioperative management of DM) patient should also receive basal insulin to prevent fluctuations in blood sugar levels or long periods of hyperglycemia without intervention
- construction of a supplemental sliding scale for a patient on anti-hyperglycemics
  - Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD)
  - BG <4: call MD and give 15 g carbohydrates
  - BG between 4 to 8: no additional insulin
  - BG between 8 to (8 + CF): give one additional unit
  - BG between (8 + CF) to (8 + 2CF): give two additional units
  - BG between (8 + 2CF) to (8 + 3CF): give three additional units

Insulin Pump Therapy (continuous subcutaneous insulin infusion [CSII])

- external battery-operated device provides constant basal dose of rapid-acting insulin analogue (aspart, glulisine, or lispro) through small subcutaneous catheter
- at meals, patient programs pump to deliver insulin bolus
- provides improved quality of life and flexibility
- risk of DKA if pump is inadvertently disconnected

Conversion Chart for Percentage HbA1c to Average Blood Sugar Control

<table>
<thead>
<tr>
<th>Average blood sugar level (mmol/L)</th>
<th>Hemoglobin A1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>12%</td>
</tr>
<tr>
<td>16</td>
<td>11%</td>
</tr>
<tr>
<td>14</td>
<td>10%</td>
</tr>
<tr>
<td>12</td>
<td>9%</td>
</tr>
<tr>
<td>10</td>
<td>8%</td>
</tr>
<tr>
<td>8</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>6%</td>
</tr>
</tbody>
</table>

The 8 Is Precipitating DKA

Infection
Ischemia or Infarction
Infotrogenic (glucocorticoids)
Intoxication
Insulin missed
Initial presentation
Intra-abdominal process
(e.g. pancreatitis, cholecystitis)
Intraoperative/perioperative stress
**Acute Complications**

### Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States

<table>
<thead>
<tr>
<th><strong>Diabetic Ketoacidosis (DKA)</strong></th>
<th><strong>Hyperosmolar Hyperglycemic State (HHS)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathophysiology</strong></td>
<td></td>
</tr>
<tr>
<td>• Usually occurs in type 1 DM</td>
<td></td>
</tr>
<tr>
<td>• Insulin deficiency with ↑ counterregulatory hormones (glucagon, cortisol, catecholamines, GH)</td>
<td></td>
</tr>
<tr>
<td>• Can occur with lack of insulin (non-adherence, inadequate dosage, 1st presentation) or increased stress (surgery, infection, exercise)</td>
<td></td>
</tr>
<tr>
<td>• Unrestricted hepatic glucose production → hyperglycemia → osmotic diuresis → dehydration and electrolyte disturbance → ↓ Na⁺ (water shift to ECF causing pseudohyponatremia)</td>
<td></td>
</tr>
<tr>
<td>• Fat mobilization → ↑ FFA → ketoadiposis → metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td>• Severe hyperglycemia exceeds the renal threshold for glucose and ketone reabsorption → glucosuria and ketonuria</td>
<td></td>
</tr>
<tr>
<td>• Total body K⁺ depletion but serum K⁺ may be normal or elevated</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td><strong>Serum</strong></td>
</tr>
<tr>
<td>• Immediate resuscitation and emergency measures if patient is stuporous or comatose</td>
<td>• ↑ BG (typically 200-1000 mg/dL, 11-55 mmol/L), ↓ Na⁺ (2º to hyperglycemia → for every ↑ in BG by 180 mg/dL (10 mmol/L) there is a ↓ in Na⁺ by 3 mEq/L)</td>
</tr>
<tr>
<td>• Monitor degree of ketoadiposis with AG, possible ↑ respiratory alkalosis</td>
<td>• ↑ BG (typically 800-2400 mg/dL, 44.4-133.2 mmol/L)</td>
</tr>
<tr>
<td>• Dehydration (orthostatic changes)</td>
<td>• In mild dehydration, may have hyponatremia (spurious ↑ to hyperglycemia → for every ↑ in BG by 180 mg/dL (10 mmol/L) there is a ↓ in Na⁺ by 3 mEq/L)</td>
</tr>
<tr>
<td>• LOC may be ↓ with ketoacidosis or with high serum osmolality (osm &gt;330 mmol/L)</td>
<td>• if dehydration progresses, may get hypernatremia</td>
</tr>
<tr>
<td>• Abdominal pain</td>
<td>• Ketoacidosis usually absent or mild if starvation occurs</td>
</tr>
<tr>
<td>• Fruity smelling breath</td>
<td>• ↑ osmolality</td>
</tr>
<tr>
<td>• Kussmaul’s respiration</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>ABG</strong></td>
</tr>
<tr>
<td>• Metabolic acidosis with ↑ AG, possible ↑ respiratory alkalosis</td>
<td>• Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI)</td>
</tr>
<tr>
<td>• If severe vomiting/dehydration there may be a metabolic alkalosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Urine</strong></td>
</tr>
<tr>
<td>• + ve for glucose and ketones</td>
<td>• - ve for ketones unless there is starvation ketosis</td>
</tr>
<tr>
<td></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>• Immediate resuscitation and emergency measures if patient is stuporous or comatose</td>
<td>• Same resuscitation and emergency measures as DKA</td>
</tr>
<tr>
<td>• Monitor degree of ketoadiposis with AG, not BG or serum ketone level</td>
<td>• Rehydration:</td>
</tr>
<tr>
<td></td>
<td>• Initial 1 L NS in 1st h</td>
</tr>
<tr>
<td></td>
<td>• after 1st 2 L, 300-400 mL/h 0.45% NaCl (continue NS if corrected sodium is falling faster than 3 mEq/kg water/h)</td>
</tr>
<tr>
<td></td>
<td>• once BG reaches 250 mg/dL (13.9 mmol/L) then switch to D5W to maintain BG in the range of 250-300 mg/dL (13.9-16.6 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>• Insulin therapy:</td>
</tr>
<tr>
<td></td>
<td>• critical to resolve acidosis, not hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>• do not use with hypokalemia, until serum K⁺ is corrected to &gt;3.3 mEq/L</td>
</tr>
<tr>
<td></td>
<td>• use only regular insulin (R)</td>
</tr>
<tr>
<td></td>
<td>• maintain on 0.1 U/kg/h insulin R infusion</td>
</tr>
<tr>
<td></td>
<td>• check serum glucose hourly</td>
</tr>
<tr>
<td></td>
<td>• K⁺ replacement:</td>
</tr>
<tr>
<td></td>
<td>• with insulin administration, hypokalemia may develop</td>
</tr>
<tr>
<td></td>
<td>• if serum K⁺ &lt;3.3 mEq/L, hold insulin and give 40 mEq/L K⁺ replacement</td>
</tr>
<tr>
<td></td>
<td>• when K⁺ &gt;3.5-5.0 mEq/L add KCl 20-40 mEq/L IV fluid to keep K⁺ in the range of 3.5-5 mEq/L</td>
</tr>
<tr>
<td></td>
<td>• HCO₃⁻:</td>
</tr>
<tr>
<td></td>
<td>• if pH &lt;7.0 or if hypotension, arrhythmia, or coma is present</td>
</tr>
<tr>
<td></td>
<td>• ↓ HCO₃⁻ → metabolic acidosis; ↑ osmolality</td>
</tr>
<tr>
<td></td>
<td>• in case of life-threatening hyperkalemia</td>
</tr>
<tr>
<td></td>
<td>• ± mannitol (for cerebral edema)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
Macrovascular Complications

- increased risk of CAD, ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- CAD (see Cardiology and Cardiac Surgery, C25)
  - risk of MI is 3–5x higher in those with DM compared to age-matched controls
  - CAD is the leading cause of death in type 2 DM
  - most patients with DM are considered “high risk” under the risk stratification for CAD (see Dyslipidemias, E2)
- ischemic stroke (see Neurology, N46)
  - risk of stroke is approximately 2.5x higher in those with DM
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - HbA1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Vascular Surgery, VS2)
  - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with DM compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with DM
- treatment
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight low density lipoprotein (LDL) cholesterol control (LDL <77 mg/dL [<2.0 mmol/L])
  - ACEI or angiotensin receptor blocker in high-risk patients
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - smoking cessation

Microvascular Complications

DIABETIC RETINOPATHY (see Ophthalmology, OP35)

Epidemiology

- type 1 DM: 25% affected at 5 yr, 100% at 20 yr
- type 2 DM: 25% affected at diagnosis, 60% between 20 yr
- leading cause of blindness in North America between the ages of 20–74
- most important factor is disease duration

Clinical Features

- nonproliferative
  - asymptomatic but if macular involvement occurs vision may be impaired
  - microaneurysms, hard exudates, dot-blot and flame hemorrhages
- preproliferative
  - macular edema, cotton wool spots, venous shunts and beading, intra-retinal microvascular abnormalities (IRMA)
- proliferative
  - with neovascularization and fibrous scarring; great risk for loss of vision secondary to vitreous hemorrhage (floaters) and/or retinal detachment

Treatment and Prevention

- tight glycemic control (delays onset, decreases progression), tight lipid control, manage HTN, smoking cessation
- pan-retinal laser photocoagulation for treatment of neovascularization
- vitrectomy
- annual follow-up visits with an optometrist or ophthalmologist examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of type 2 DM; 5 yr after diagnosis of type 1 DM)
- interval for follow-up should be tailored to severity of retinopathy
DIABETIC NEPHROPATHY (see Nephrology, NP28)

Epidemiology
- DM-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with type 1 DM (after 5-10 yr) and 4-20% with type 2 DM have progressive nephropathy

Pathophysiology
- thickening of capillary basement membrane and glomerular mesangium resulting in glomerulosclerosis and renal insufficiency
- diffuse glomerulosclerosis is more common than nodular intercapillary glomerulosclerosis (Kimmelstiel-Wilson lesions)

Screening
- serum creatinine
- random urine test for albumin to creatinine ratio (ACR) plus urine dipstick test for all type 2 DM patients at diagnosis, then annually, and for postpubertal type 1 DM patients with ≥5 yr duration of DM

Clinical Features
- initial changes include microalbuminuria, increased GFR (up to 140%) from hyperfiltration, enlarged kidneys
- microalbuminuria: 30 μg/mg
- macroalbuminuria: 300 μg/mg
- progression over 15 yr to cause HTN, persistent proteinuria (macroalbuminuria), nephrotic syndrome, and renal failure
- elevated HbA1c is an independent risk factor for progression to microalbuminuria

Treatment and Prevention
- tight glycemic control
- tight blood pressure control (<130/80 mmHg): can use either ACEI or ARB (often used first line for their CVD protection)
- even in the absence of glycemic control ACEIs or ARBs reduce the level of albuminuria and the rate of progression of renal disease in normotensive and hypertensive patients with type 1 or type 2 DM
- type 1 DM → CKD with either HTN or albuminuria → ACEIs 1st line; ARBs 2nd line
- type 2 DM → CKD with HTN and albuminuria → ACEIs or ARBs (dose adjust if creatinine clearance (CrCl) <60 mL/min)
- consider use of non-dihydropyridine calcium channel blocker (e.g. diltiazem) in those unable to tolerate both ACEIs and ARBs
- limit use of nephrotoxic drugs and dyes
- renal failure may necessitate hemodialysis and renal transplant

DIABETIC NEUROPATHY (see Neurology, N42)

Epidemiology
- approximately 50% of patients within 10 yr of onset of type 1 DM and type 2 DM

Pathophysiology
- can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy
- mechanism poorly understood
- acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerve
- the more common motor and sensory neuropathies are thought to be related to metabolic or osmotic toxicity secondary to increased sorbitol and/or decreased myoinositol (possible mechanisms include accumulation of advanced glycation endproducts [AGE], oxidative stress, protein kinase C, nerve growth factor deficiency)

Screening
- 128 Hz tuning fork or 10 g monofilament at diagnosis and annually in people with type 2 DM and after 5 yr duration of type 1 DM

Management of Diabetic Retinopathy: A Systematic Review
JAMA 2007;298:902-916

Purpose: To review the best evidence for primary and secondary interventions in the management of diabetic retinopathy (DR), including diabetic macular edema.

Study Selection: English-language RCTs with more than 12 mo of follow-up and meta-analyses were included.

Results: Forty-four studies (including 3 meta-analyses) met the inclusion criteria. Tight glycemic and blood pressure control reduces the incidence and progression of DR. Pan-retinal laser photocoagulation reduces the risk of moderate and severe visual loss by 50% in patients with severe nonproliferative and proliferative retinopathy. Focal laser photocoagulation reduces the risk of moderate visual loss by 50-70% in eyes with macular edema. Early vitrectomy improves visual recovery in patients with proliferative retinopathy and severe vitreous hemorrhage. Intravitreal injections of steroids may be considered in eyes with persistent loss of vision when conventional treatment has failed.

Conclusions: Tight glycemic and blood pressure control remains the cornerstone in the primary prevention of DR. Pan-retinal and focal retinal laser photocoagulation reduces the risk of visual loss in patients with severe DR and macular edema, respectively. There is currently insufficient evidence to recommend routine use of other treatments.
Clinical Features

Table 13. Clinical Presentation of Diabetic Neuropathies

<table>
<thead>
<tr>
<th>Peripheral Sensory Neuropathy</th>
<th>Motor Neuropathy</th>
<th>Autonomic Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation</td>
<td>Less common than sensory neuropathy</td>
<td>Postural hypotension, tachycardia, decreased cardiovascular response to Valsalva maneuver</td>
</tr>
<tr>
<td>Blateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands</td>
<td>Delayed motor nerve conduction and muscle weakness/atrophy</td>
<td>Gas troparexis and alternating diarrhea and constipation</td>
</tr>
<tr>
<td>Decreased ankle reflex</td>
<td>May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex)</td>
<td>Urinary retention and erectile dysfunction</td>
</tr>
<tr>
<td>Symptoms may first occur in entrapment syndromes e.g. carpal tunnel</td>
<td>Some of the motor neuropathies spontaneously resolve after 6-8 wk</td>
<td></td>
</tr>
<tr>
<td>May result in neuropathic ulceration of foot</td>
<td>Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell’s palsy)</td>
<td></td>
</tr>
<tr>
<td>Diabetic amyotrophy: refers to pain, weakness, and wasting of hip flexors or extensors</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment and Management

- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anti-epileptics (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), erythromycin (stimulates motilin receptors)
- medical, mechanical, and surgical treatment for erectile dysfunction (see Urology, U30)

Other Complications

Dermatologic

- diabetic dermopathy: atrophic brown spots commonly in pretibial region known as “shin spots”, secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the shins allowing visualization of subcutaneous vessels

Bone and Joint Disease

- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren’s contracture
- bone demineralization: bone density 10-20% below normal
- adhesive capsulitis (“frozen shoulder”)

Cataracts

- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

Infections

- see Infectious Diseases, ID16

Hypoglycemia

Etiology and Pathophysiology

- hypoglycemia occurs most frequently in people with DM receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without DM, care must be taken to distinguish fasting from post-prandial hypoglycemia as each invokes separate differential diagnoses

Effects of Treatments for Symptoms of Painful Diabetic Neuropathy: Systematic Review

**Purpose:** To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.

**Study Selection:** RCTs comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.

**Results:** 25 included reports compared anticonvulsants (n=1,270), antidepressants (94), opioids (329), ion channel blockers (173), NMDA antagonist (14), duloxetine (65), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% CI 1.77-16.02) for traditional anticonvulsants, 3.25 (95% CI 2.27-4.68) for newer generation anticonvulsants, and 2.24 (95% CI 9.83-64.74) for tricyclic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (95% CI 0.33-6.96) for traditional anticonvulsants, 2.98 (95% CI 1.79-5.07) for newer generation anticonvulsants, and 2.32 (95% CI 0.59-9.69) for tricyclic antidepressants.

**Conclusion:** Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Tricyclic antidepressants and traditional anticonvulsants are better for short-term pain relief than newer anticonvulsants. Evidence of the long-term effects of antidepressants and anticonvulsants is lacking. Further studies are needed on opioids, NMDA antagonists, and ion channel blockers.

C-Peptide

A short peptide released into the circulation when proinsulin is cleaved to insulin

Other Players in Glucose Homeostasis

These hormones act to increase blood glucose levels

- Glucagon
- Epinephrine
- Cortisol
- Growth hormone

C-Peptide

A short peptide released into the circulation when proinsulin is cleaved to insulin
Clinical Features

- Whipple’s triad
  1. serum glucose 45 mg/dL (<2.5 mmol/L) in males and 40 mg/dL (<2.2 mmol/L) in females
  2. neuroglycopenic symptoms
  3. rapid relief provided by administration of glucose
- adrenergic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia
- neuroglycopenic symptoms (caused by decreased activity of CNS)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations

- electrolytes, creatinine, LFTs, drugs/toxins, cortisol
- if concerned about possible insulinoma:
  - blood work to be drawn when patient is hypoglycemic (e.g. during hospitalized 72 h fast)
  - may need ongoing glucose infusion once BG > 90 mg/dL (5 mmol/L)

Treatment

- for fasting hypoglycemia, must treat underlying cause
- for post-prandial (reactive) hypoglycemia, frequent small feeds
- see Emergency Medicine, EM36
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV or 1 mg glucagon SC (if no IV available)
  - blood work to be drawn when patient is hypoglycemic (e.g. during hospitalized 72 h fast)
- repeat steps 1-3 until BG > 90 mg/dL
  - 1) Eat 15 g of carbohydrates (CHO)
  - 2) Wait 15 min
  - 3) Retest Blood Glucose (BG)
  - 4) Repeat steps 1-3 until BG > 90 mg/dL
  - 5) Eat next scheduled meal. If next meal is > 1 h away, eat snack including 15 g of CHO and protein.

Metabolic Syndrome

- several definitions, most widely used are National Cholesterol Education Program (NCEP/ATP III, updated by American Heart Association) and International Diabetes Federation (IDF) definitions
- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, HTN, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include DM, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Obesity

- see Family Medicine, FM7
Pituitary Gland

Pituitary Hormones

Hypothalamic-pituitary hormonal axes
CRH = corticotropin-releasing hormone; GnRH = gonadotropin-releasing hormone; GHIH = growth hormone-inhibiting hormone; GHRH = growth hormone-releasing hormone; PRH = prolactin-releasing hormone; TRH = thyrotropin-releasing hormone

Hypothalamic Control of Pituitary
- trophic and inhibitory factors control the release of pituitary hormones
- most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control by dopamine, as well as GH and TSH which are inhibited by SS (somatostatin)
- transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

Anterior Pituitary Hormones
- growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and prolactin (PRL)

Posterior Pituitary (Hypothalamic) Hormones
- antidiuretic hormone (ADH) and oxytocin
- peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
- although ADH and oxytocin are produced in the hypothalamus these hormones are stored and released from the posterior pituitary

Table 15. The Physiology and Action of Pituitary Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>• Stimulates growth of adrenal cortex and secretion of its hormones</td>
<td>• Polypeptide • Pulsatile and diurnal variation (highest in AM, lowest at midnight)</td>
<td>• Dexamethasone • Cortisol</td>
<td>• CRH • Metyrapone • Insulin-induced hypoglycemia • Vasopressin • Fever, pain, stress</td>
</tr>
<tr>
<td>GH</td>
<td>• Needed for linear growth • IGF-1 stimulates growth of bone and cartilage</td>
<td>• Polypeptide • Acts indirectly through serum factors synthesized in the liver; IGF-1 (somatomedin-C) • Serum GH undetectable for most of the day and suppressed after meals high in glucose • Sustained rise during sleep</td>
<td>• Glucose challenge • Glucocorticoids • Hypothyroidism • Somatostatin • Dopamine D2 receptor agonists • IGF-1 (long-loop) • Tonically by dopamine</td>
<td>• GHHR • Insulin-induced hypoglycemia • Exercise • REM sleep • Arginine, clonidine, propranolol, L-dopa</td>
</tr>
</tbody>
</table>
### Table 15. The Physiology and Action of Pituitary Hormones (continued)

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH/FSH</td>
<td>• Stimulate gonads via cAMP • Ovary: – LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles – FSH: growth of granulosa cells in ovarian follicle; controls estrogen formation • Testes: – LH: production of testosterone (Leydig cells) – FSH: production of spermatozoa (Sertoli cells)</td>
<td>• Polypeptide • Glycoproteins (similar α subunit as TSH and hCG) • Secreted in pulsatile fashion</td>
<td>• Estrogen • Progesterone • Testosterone • Inhibin • Continuous (i.e. non-pulsatile) GnRH infusion</td>
<td>• Pulsatile GnRH</td>
</tr>
<tr>
<td>Prolactin</td>
<td>• Promotes milk production • Inhibits GnRH secretion</td>
<td>• Polypeptide • Episodic secretion</td>
<td>• Dopamine</td>
<td>• Sleep • Stress, hypoglycemia • Pregnancy, breastfeeding • Mid-menstrual cycle • Sexual activity • TRH • Drugs: psychotropics, antihypertensives, dopamine antagonists, opiates, high dose estrogen</td>
</tr>
<tr>
<td>TSH</td>
<td>• Stimulates growth of thyroid and secretion of T3 and T4 via cAMP</td>
<td>• Glycoprotein</td>
<td>• Circulating thyroid hormones (T3, T4) • Opiates, dopamine</td>
<td>• TRH • Epinephrine • Prostaglandins</td>
</tr>
<tr>
<td>ADH</td>
<td>• Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine</td>
<td>• Octapeptide • Secreted by posterior pituitary • Osmoreceptors in hypothalamus detect serum osmolality • Contracted plasma volume detected by baroreceptors is a more potent stimulus than T osmolality</td>
<td>• ↓ serum osmolality</td>
<td>• Hyponatremia or ↓ effective circulatory volume • ↑ serum osmolality • Stress, pain, fever, paraneoplastic • Lung or brain pathology</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>• Causes uterine contraction • Breast milk secretion</td>
<td>• Not a peptide • Secreted by posterior pituitary</td>
<td>• ΕΩH</td>
<td>• Suckling • Distention of female genital tract during labor via stretch receptors</td>
</tr>
</tbody>
</table>

### Growth Hormone

**GH DEFICIENCY**
- cause of short stature in children (see Pediatrics, P27)
- controversial significance in adults; often not clinically apparent, may present as fatigue

**GH EXCESS**
- in children (before epiphyseal fusion) leads to gigantism
- in adults (after epiphyseal fusion) leads to acromegaly

**Etiology**
- GH secreting pituitary adenoma, carcinoid or pancreatic islet tumors secreting ectopic GHRH resulting in excess GH

**Pathophysiology**
- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in growth hormone excess states secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

**Clinical Features**
- enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, thickening of skin, increased sebum production, sweating, acne, sebaceous cysts, fibromata mollusca, acanthosis nigricans, arthralgia, carpal tunnel syndrome, degenerative osteoarthritis, thyromegaly, renal calculi, HTN, cardiomyopathy, obstructive sleep apnea, colonic polyps, and DM

**Signs and Symptoms of Acromegaly:**
- ABCDEF
- Abnormal gait
- Blood pressure raised
- Carpal tunnel syndrome
- Diabetes
- Enlarged organs
- Field defect (visual)
Investigations
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- elevated serum insulin-like growth factor-1 (IGF-1) is usually first line diagnostic test

Treatment
- surgery, octreotide (somatostatin analogue), dopamine agonist (bromocriptine/cabergoline), growth hormone receptor antagonist (pegvisomant), radiation

Prolactin

HYPERPROLACTINEMIA

Etiology
- pregnancy and breastfeeding
- prolactinoma: most common pituitary adenoma (prolactin-secreting tumors may be induced by estrogens and grow during pregnancy)
- pituitary masses with pituitary stalk compression causing reduced dopamine inhibition of prolactin release
- primary hypothyroidism (increased TRH)
- decreased clearance due to chronic renal failure or severe liver disease (prolactin is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics (common), antidepressants, antihypertensives, anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide/domperidone), H2-blockers (ranitidine)
- macroprolactinemia (high molecular weight prolactin also known as big big prolactin)

Clinical Features
- galactorrhea (secretion of breast milk in women and, in rare cases, men), infertility, hypogonadism, amenorrhea, erectile dysfunction

Investigations
- serum PRL, TSH, liver enzyme tests, creatinine
- MRI of the sella turcica

Treatment
- long-acting dopamine agonist: bromocriptine, cabergoline, or quinagolide (Norprolac®)
- surgery ± radiation (rare)
- prolactin-secreting tumors are very slow-growing and sometimes require no treatment
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

Thyroid Stimulating Hormone

- see Thyroid, E20

Adrenocorticotropic Hormone

- see Adrenal Cortex, E29

Luteinizing Hormone and Follicle Stimulating Hormone

- see Gynecology, GY4

HYPOGONADOTROPIC HYPOGONADISM

Clinical Features
- hypogonadism, amenorrhea, erectile dysfunction (see Urology, U30), loss of body hair, fine skin, testicular atrophy, failure of pubertal development

Treatment
- Pergonal® (combined FSH/LH hormone therapy), hCG, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

HYPERGONADOTROPIC HYPOGONADISM
- 2nd hypersecretion in gonadal failure (e.g. in menopause)
Antidiuretic Hormone

DIABETES INSIPIDUS

Definition
• disorder of ineffective ADH (decreased production or peripheral resistance) resulting in passage of large volumes of dilute urine

Etiology and Pathophysiology
• central DI: insufficient ADH due to pituitary surgery, tumors, idiopathic/autoimmune, stalk lesion, hydrocephalus, histiocytosis X, trauma, familial central DI
• nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI
• psychogenic polydipsia and osmotic diuresis must be ruled out

Clinical Features
• passage of large volumes of dilute urine, polydipsia, and dehydration; hypernatremia can develop with inadequate water consumption or secondary to an impaired thirst mechanism

Diagnostic Criteria
• fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
• response to exogenous ADH (DDAVP) will distinguish central from nephrogenic DI

Treatment
• DDAVP/vasopressin for central DI
• chlorpropamide, clofibrate, thiazides, NSAIDs, or carbamazepine as second line or for partial DI
• nephrogenic DI treated with solute restriction NSAIDs and thiazide diuretics; DDAVP (if partial)

SYNDROME OF INAPPROPRIATE ADH SECRETION

Diagnostic Criteria
• hyponatremia with corresponding plasma hypo-osmolality, urine sodium concentration above 40 mEq/L, urine less than maximally diluted (>100 mOsm/kg), euvolemia (edema absent), and absence of adrenal, renal, or thyroid insufficiency

Etiology and Pathophysiology
• stress (pain, nausea, post-surgical)
• malignancy (lung, pancreas, lymphoma)
• CNS disease (inflammatory, hemorrhage, tumor, Guillain-Barré syndrome)
• respiratory disease (TB, pneumonia, empyema)
• drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

Treatment
• treat underlying cause, fluid restriction (800-1000 mL/day), vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), and demeclocycline (antibiotic with anti-ADH properties, rarely-used) fludrocortisone, furosemide

Pituitary Pathology

PITUITARY ADENOMA (see Neurosurgery, NS13)

Clinical Features
• local mass effects
  • visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies), headaches; increased ICP is rare
  • hypofunction
  • hypopituitarism
  • hyperfunction
  • PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing’s disease = Cushing’s syndrome caused by a pituitary tumor)
  • tumors secreting LH, FSH, and TSH are rare

Investigations
• radiological evaluation (MRI is imaging procedure of choice)
• formal visual field testing
• hypothalamic-pituitary hormonal function
HYPOPITUITARISM

Etiology (the eight Is)
- Invasive
  - pituitary tumors, craniopharyngioma, cysts (Rathke's cleft, arachnoid, or dermoid), metastases
- Infarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive post-partum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumor; presents with sudden loss of pituitary hormones, severe headache, and altered level of consciousness; can be fatal if not recognized and treated early)
- Infiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- Infectious
  - syphilis, TB, fungal (histoplasmosis), parasitic (toxoplasmosis)
- Injury
  - severe head trauma
- Immunologic
  - autoimmune destruction
- Iatrogenic
  - following surgery or radiation
- Idiopathic
  - familial forms, congenital midline defects

Investigations
- triple bolus test
  - stimulates release of all anterior pituitary hormones in normal individuals
  - rapid sequence of IV infusion of insulin, GnRH, and TRH
    - insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and ACTH
    - GnRH (100 µg IV push) → increased LH and FSH
    - TRH (200 µg IV push over 120 s) → increased TSH and PRL (no longer available)

Thyroid

Thyroid Hormones

Synthetic Function of Thyroid Gland
- the synthesis of thyroid hormones $T_3$ (thyroxine) and $T_4$ (triiodothyronine) by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, and release of $T_3$ and $T_4$
• free T<sub>3</sub> (0.03%) and free T<sub>4</sub> (0.3%) represent the hormonally active fraction of thyroid hormones
  ▪ the remaining fraction is bound to thyroxine binding globulin (TBG) and albumin and is biologically inactive
• T<sub>3</sub> is more biologically active (3-8x more potent), but T<sub>4</sub> has a longer half-life
• 85% of T<sub>4</sub> is converted to T<sub>3</sub> or reverse T<sub>3</sub> (RT3) in the periphery by deiodinases
• RT3 is metabolically inactive but produced in times of stress to decrease metabolic activity
• most of the plasma T<sub>3</sub> pool is derived from the peripheral conversion of T<sub>4</sub>
• calcitonin, a peptide hormone, is also produced in the thyroid, by the parafollicular cells or C cells
  ▪ it functions by inhibiting osteoclast activity and increasing renal calcium excretion

Role of Thyroid Hormones
• thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
• action of these hormones is diffuse, effecting nearly every organ system
• they produce an increase in basal metabolic rate including: increased Na<sup>+</sup>/K<sup>+</sup> ATPase activity, increased O<sub>2</sub> consumption, increased respiration, heat generation, and increased cardiovascular activity
• also play crucial role during fetal life in both neurological and somatic development

Regulation of Thyroid Function
• extrathyroid
  ▪ stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
  ▪ T<sub>3</sub> negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
• intrathyroid (autoregulation)
  ▪ synthesis (Wolff-Chaikoff effect, Jod-Basedow effect)
  ▪ there is varying thyroid sensitivity to TSH in response to iodide availability
  ▪ increased ratio of T<sub>3</sub> to T<sub>4</sub> in iodide deficiency
  ▪ increased activity of peripheral 5' deiodinase in hypothyroidism increases T<sub>3</sub> production despite low T<sub>4</sub> levels

Tests of Thyroid Function and Structure

TSH
• sensitive TSH (sTSH) is the best test for assessing thyroid function
• hyperthyroidism
  ▪ primary: TSH is low because of negative feedback from increased levels of circulating T<sub>3</sub> and T<sub>4</sub>
  ▪ secondary: increased TSH results in increased T<sub>3</sub> and T<sub>4</sub>
• hypothyroidism
  ▪ primary: increased TSH (most sensitive test) because of less negative feedback from T<sub>3</sub> and T<sub>4</sub>
  ▪ secondary: TSH is low or normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T<sub>3</sub> and Free T<sub>4</sub>
• standard assessment of thyroid function measures TSH and if necessary free T<sub>3</sub>. free T<sub>4</sub> should be measured if TSH is suppressed and free T<sub>4</sub> is normal to rule out T<sub>3</sub> toxicity

Thyroid Autoantibodies
• anti-thyroglobulin antibodies (TgAb), anti-thyroid peroxidase antibodies, anti-TSH-receptor inhibiting antibodies
  ▪ increased in Hashimoto’s disease; normal variant in 10-20% of individuals
• thyroid stimulating immunoglobulin (TSI)/TSH receptor stimulating antibodies

Plasma Calcitonin
• used to monitor for residual thyroid tissue post-thyroidectomy, e.g. tumor marker for thyroid cancer recurrence
• normal or elevated levels may suggest persistent, recurrent, or metastatic disease

Serum Calcitonin
• not routinely done to investigate thyroid nodules
• ordered if suspicion of medullary thyroid carcinoma or family history of MEN IIa or IIb syndromes
• used to monitor for residual or recurrent medullary thyroid cancer

Thyroid Imaging/Scans
• normal gland size 15-20 g (estimated by palpation)
• thyroid U/S
  ▪ to measure size of gland, solid vs. cystic nodule, facilitate fine needle aspirate biopsy (FNAB)
• radioisotope thyroid scan (Technetium-99)
  ▪ test of structure: order if there is a thyroid nodule and patient is hyperthyroid with low TSH
  ▪ differentiates between hot (functioning → excess thyroid hormone production) and cold (non-functioning) nodules
    ▪ hot nodule → very low chance malignancy; treat hyperthyroidism
    ▪ cold nodule → ~5% chance malignancy; further workup required (U/S and FNAB)

### Patterns of Hormone Levels

<table>
<thead>
<tr>
<th></th>
<th>TSH</th>
<th>T&lt;sub&gt;3&lt;/sub&gt;</th>
<th>T&lt;sub&gt;4&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Hyper</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>2° Hyper</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>1° Hypo</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>2° Hypo</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
</tbody>
</table>

### Weight Reference

- **LR+**: 0.20-0.30
- **LR-**: 0.80-0.90

<table>
<thead>
<tr>
<th>Weight (g)</th>
<th>Reference</th>
<th>LR+ (95% CI)</th>
<th>LR- (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20 g</td>
<td>normal</td>
<td>0.15 (0.10-0.21)</td>
<td>1.0 (0.1-10)</td>
</tr>
<tr>
<td>20-40 g</td>
<td>1x</td>
<td>1.9 (1.1-3.5)</td>
<td>0.9 (0.1-10)</td>
</tr>
<tr>
<td>&gt;40 g</td>
<td>2x</td>
<td>25.0 (2.6-175)</td>
<td>0.15 (0.1-1.0)</td>
</tr>
</tbody>
</table>

Alternatively, defining a goiter as mass larger than 40 g >2x 25.0 (2.6-175) and <40 g <2x 25.0 (0.1-2.6) has a LR+ of 3.0 (95% CI 2.5-3.5) and LR- of 0.30 (95% CI 0.24-0.37) in children, and an LR+ of 4.7 (95% CI 3.6-6.0) and LR- of 0.08 (95% CI 0.02-0.27) for the presence of a goiter.

Conclusions: Use of weight of thyroid tissue is an appropriate method of diagnosing a goiter, while comparing the size of thyroid mass to the distal phalanx of the thumb has been shown to have an LR+ of 3.6-6.0 (2.6-175) and LR- of 0.08 (0.02-0.27) for the presence of a goiter.

### Thyroid Assessment
- Serum thyroid hormones (TSH, T<sub>3</sub>, T<sub>4</sub>)
- Antibodies
- Thyroglobulin (to monitor thyroid cancer)
- Thyroid U/S
- Nuclear uptake and scan (for hyperthyroidism)
- Biopsy (FNA)
radioactive iodine uptake (RAIU)
- test of function: order if patient is thyrotoxic
- RAIU measures the turnover of iodine by thyroid gland in vivo
- if ↑ uptake (i.e. incorporated) → gland is overactive (hyperthyroid)
- if ↓ uptake (i.e. not incorporated) → gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)

• see Figure 8, Approach to the Evaluation of a Thyroid Nodule, E29 for further information regarding the utility of these scans

Thyroid Biopsy
- fine needle aspiration (FNA) for cytology
  - differentiates between benign and malignant disease
  - best done under U/S guidance
  - accuracy decreased if nodule is greater than 50% cystic, or if nodule located posteriorly in the gland

Table 16. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TSH</strong></td>
<td>Increased in 1° hyperthyroidism</td>
<td>Increased in 1° hypothyroidism</td>
</tr>
<tr>
<td><strong>Free T₄</strong></td>
<td>Increased in 1° hyperthyroidism</td>
<td>Increased in 1° hypothyroidism</td>
</tr>
<tr>
<td><strong>Antibodies</strong></td>
<td>Graves': thyroid stimulating Ig (TSI)</td>
<td>Decreased uptake</td>
</tr>
<tr>
<td><strong>RAIU</strong></td>
<td>Graves', Toxic multinodular goiter, Toxic adenoma</td>
<td>Subacute thyroiditis</td>
</tr>
<tr>
<td><strong>Radioisotope</strong></td>
<td>Graves': homogenous diffuse uptake</td>
<td>Recent iodine load</td>
</tr>
<tr>
<td><strong>Thyroid Scan</strong></td>
<td>Multinodular goiter: heterogenous uptake</td>
<td>Exogenous thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>Toxic adenoma: single intense area of uptake with suppression elsewhere</td>
<td></td>
</tr>
</tbody>
</table>

Thyrotoxicosis

Definition
- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

Epidemiology
- 1% of general population have hyperthyroidism
- F:M = 5:1

Etiology and Pathophysiology

Table 17. Differential Diagnosis of Thyrotoxicosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>Free T₄/T₃</th>
<th>Thyroid Antibodies</th>
<th>RAIU</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPERTHYROIDISM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves' Disease</td>
<td>Decreased</td>
<td>Increased</td>
<td>TSI</td>
<td>Increased</td>
<td>Heterogeneous uptake on scan</td>
</tr>
<tr>
<td>Toxic Nodular Goiter</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Heterogeneous uptake on scan</td>
</tr>
<tr>
<td>Toxic Nodule</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Intense uptake in hot nodule on scan with no uptake in the rest of the gland</td>
</tr>
<tr>
<td><strong>THYROIDITIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute, Silent, Postpartum</td>
<td>Decreased</td>
<td>Increased</td>
<td>Up to 50% of cases</td>
<td>Decreased</td>
<td>Increased once entering hypothyroid phase, when TSH rises</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In classical subacute painful thyroiditis, ESR increased</td>
</tr>
<tr>
<td><strong>EXTRATHYROIDAL SOURCES OF THYROID HORMONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Exogenous (drugs)</td>
<td>Decreased</td>
<td>Increased</td>
<td>(T₄ would be decreased if taking T₃)</td>
<td>None</td>
<td>Decreased</td>
</tr>
</tbody>
</table>
Table 17. Differential Diagnosis of Thyrotoxicosis (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>Free T&lt;sub&gt;4&lt;/sub&gt;/T&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Thyroid Antibodies</th>
<th>RAIU</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXCESSIVE THYROID STIMULATION</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary thyrotrophoma</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Pituitary thyroid hormone receptor resistance</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Increased hCG (e.g. pregnancy)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td><strong>DO NOT DO THIS TEST IN PREGNANCY</strong></td>
</tr>
</tbody>
</table>

Clinical Features

Table 18. Clinical Features of Thyrotoxicosis

<table>
<thead>
<tr>
<th>General</th>
<th>Fatigue, heat intolerance, irritability, fine tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Tachycardia, atrial fibrillation, palpitations</td>
</tr>
<tr>
<td>GI</td>
<td>Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation)</td>
</tr>
<tr>
<td>Neurology</td>
<td>Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians)</td>
</tr>
<tr>
<td>GU</td>
<td>Oligomenorrhea, amenorrhea, decreased fertility</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer’s nails), palmar erythema, paresthesia</td>
</tr>
<tr>
<td>Graves' disease: clubbing (acropachy), pretibial myxedema (rare)</td>
<td></td>
</tr>
<tr>
<td>MSK</td>
<td>Decreased bone mass, proximal muscle weakness</td>
</tr>
<tr>
<td>Hematology</td>
<td>Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally)</td>
</tr>
<tr>
<td>Eye</td>
<td>Graves' disease: lid lag, retraction, proptosis, dioplia, decreased acuity, puffiness, conjunctival injection</td>
</tr>
</tbody>
</table>

Treatment

- thionamides: PTU or MMI; MMI recommended (except in first trimester pregnancy)
- β-blockers for symptom control
- radioactive iodine thyroid ablation for Graves' disease
- surgery in the form of hemi, sub-total, or complete thyroidectomy

Graves’ Disease

Definition

- an autoimmune disorder characterized by autoantibodies to the TSH receptor that leads to hyperthyroidism

Epidemiology

- most common cause of thyrotoxicosis
- occurs at any age with peak in 3rd and 4th decade
- F>M = 7:1, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA B8 and DR3
- may be associated with other inherited autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathophysiology

- autoimmune disorder due to a defect in T-suppressor cells
- B lymphocytes produce TSI that binds and stimulates the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, lithium therapy, viral or bacterial infections, glucocorticoid depletion (an acute phase response) of TSH, resulting in increased tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbitis leads to fluid accumulation and displacement of the eye ball forward
- dermopathy may be related to cutaneous glycosaminoglycan deposition

Clinical Features

- signs and symptoms of thyrotoxicosis
- diffuse thyroid goiter ± thyroid bruit secondary to increased blood flow through the gland
- ophthalmopathy: proptosis, dioplia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity if Graves’ (plus signs of hyperthyroidism: lid retraction, characteristic stare)
• risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively

Investigations
• low TSH
• increased free T4 (and/or increased T3)
• positive for TSI
• increased radioactive iodine (I-131) uptake
• homogeneous uptake on thyroid scan (only do this test in the presence of nodule)

Treatment
• thionamides
  - propylthiouracil (PTU) or methimazole (MMI)
  - inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organization of iodide, blocking the coupling of iodotyrosines
  - PTU also inhibits peripheral deiodination of T4 to T3
  - continue treatment until remission occurs (20-40% of patients achieve spontaneous remission at 6-18 mo of treatment)
  - small goiter and recent onset are good indicators for long-term remission with medical therapy
  - major side effects: hepatitis, agranulocytosis, and fever/arthralgias
  - minor side effects: rash
  - iodinated contrast agents: sodium ipodate and iopanoic acid can inhibit conversion of T4 to T3 and are especially effective in combination with MMI
  - MMI preferred vs. PTU due to longer duration of action (once daily for most), more rapid efficacy, and lower incidence of side effects
  - MMI contraindicated in pregnancy (teratogenic), use PTU
• β-blockers
• thyroid ablation with radioactive 131I if PTU or MMI trial does not produce disease remission
  - high incidence of hypothyroidism after 131I requiring lifelong thyroid hormone replacement
  - contraindicated in pregnancy
  - may worsen ophthalmopathy
• subtotal or total thyroidectomy (indicated rarely for large goiters, suspicious nodule for CA, if patient is intolerant to thionamides and refusing RAI ablation)
• ophthalmopathy/orbitopathy
  - smoking cessation is most important
  - prevent drying
  - high dose prednisone in severe cases
  - orbital radiation, surgical decompression

Prognosis
• course remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
• lifetime follow-up needed
• risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively

Subacute Thyroiditis (Thyrotoxic Phase)

Definition
• acute inflammatory disorder of the thyroid gland characterized by an initial thyrotoxic state followed by hypothyroidism eventually followed by euthyroidism in most cases
• two subtypes: painful and painless

Etiology and Pathophysiology
• acute inflammation of the thyroid gland characterized by giant cells and lymphocytes
• disruption of thyroid follicles by inflammatory process results in the release of stored hormone rather than excessive production of new thyroid hormone
• painful = viral (usually preceded by URTI), De Quervain’s (granulomatous thyroiditis)
• painless = postpartum, auto-immune, lymphocytic
  - occurs in 5-10% of postpartum mothers and is symptomatic in 1/3 of patients

Clinical Features
• two forms
  - painful (“De Quervain’s”) thyroid, ears, jaw, and occiput
  - painless (“Silent”)
• fever and malaise may be present, especially in De Quervain’s
• postpartum: thyrotoxicosis 2-3 mo postpartum with a subsequent hypothyroid phase at 4-8 mo postpartum
• may be mistakenly diagnosed as postpartum depression

Laboratory Investigations
• initial elevated free T₄, T₃, low TSH, RAIU markedly reduced
• marked elevation of ESR in painful variety only
• as disease progresses values consistent with hypothyroidism may appear

Treatment
• painful – high dose NSAIDs, prednisone may be required for severe pain, fever, or malaise
• iodinated contrast agents (e.g. iopanoic acid, ipodate) to inhibit peripheral conversion of T₄ to T₃
• β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms in both subtypes
• if symptomatically hypothyroid, may treat short-term with thyroxine

Prognosis
• full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis
• postpartum: most resolve spontaneously without need for supplementation, however may recur with subsequent pregnancies

Toxic Adenoma/Toxic Multinodular Goiter

Etiology and Pathophysiology
• autonomous thyroid hormone production from a functioning adenoma that is hypersecreting T₃ and T₄
• may be singular (toxic adenoma) or multiple (toxic multinodular goiter [Plummer’s disease])

Clinical Features
• goiter with adenomatous changes
• tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
• seen most frequently in elderly people, often with presentation of atrial fibrillation

Investigations
• low TSH, high T₃ and T₄
• thyroid scan with increased uptake in nodule(s) and suppression of the remainder of the gland

Treatment
• initiate therapy with PTU or MMI to attain euthyroid state
• use high dose radioactive iodine (I-131) to ablate hyperfunctioning nodules
• β-blockers often necessary for symptomatic treatment prior to definitive therapy
• surgical excision may also be used as 1st line treatment

Thyrotoxic Crisis/Thyroid Storm

Definition
• acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism – medical emergency
• rare, but serious with mortality rate between 20-30%

Etiology and Pathophysiology
• often precipitated by infection, trauma, or surgery in a hyperthyroid patient

Differential Diagnosis
• sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

Clinical Features
• hyperthyroidism
• extreme hyperthermia, tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
• tachyarrhythmia, CHF, shock
• mental status changes ranging from delirium to coma
Laboratory Investigations
- increased free T₃ and T₄, undetectable TSH
- ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

General Measures
- fluids, electrolytes, and vasopressor agents should be used as indicated
- a cooling blanket and acetaminophen can be used to treat the pyrexia
- propranolol or similar agents for beta-adrenergic blockade is used, which additionally causes decreased peripheral conversion of T₄ → T₃
  - use with caution in CHF patients as it may worsen condition

Specific Measures
- PTU is the anti-thyroid drug of choice and is used in high doses
- Give iodide, which acutely inhibits the release of thyroid hormone, 1 h after the first dose of PTU is given
  - Sodium iodide 1 gm IV drip over 12h q12h
  - Lugol's solution 2-3 drops q8h
  - Potassium iodide (SSKI) 5 drops q8h
- dexamethasone 2-4 mg IV q6h for the first 24-48 h lowers body temperature and inhibits peripheral conversion of T₄ → T₃

Prognosis
- probably <20% mortality rate if rapidly recognized and treated

Hypothyroidism

Definition
- clinical syndrome caused by cellular responses to insufficient thyroid hormone production

Epidemiology
- 2-3% of general population
- F:M = 10:1
- 10-20% of women over age 50 have subclinical hypothyroidism (normal T₄, TSH mildly elevated)
- iodine deficiency most common cause worldwide, but not in North America

Etiology and Pathophysiology
- primary hypothyroidism (90%)
  - inadequate thyroid hormone production secondary to intrinsic thyroid defect
  - iatrogenic: post-ablative (¹³¹I or surgical thyroidectomy)
  - autoimmune: Hashimoto's thyroiditis, chronic thyroiditis, idiopathic, burnt out Graves'
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4,000 births)
  - neoplasia
- secondary hypothyroidism: pituitary hypothyroidism
- insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
- decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

<table>
<thead>
<tr>
<th>Table 19. Interpretation of Serum TSH and Free T₄ in Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum TSH</td>
</tr>
<tr>
<td>Overt Primary Hypothyroidism</td>
</tr>
<tr>
<td>Subclinical Primary Hypothyroidism</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
</tr>
</tbody>
</table>

Thyroid Hormone Replacement for Subclinical Hypothyroidism


Purpose: To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.

Study Selection: RCTs comparing thyroid hormone replacement with placebo in adults with subclinical hypothyroidism. Minimum duration of follow-up was 1 mo.

Results: No trial assessed (cardiovascular) mortality or morbidity. Seven studies evaluated symptoms, mood, and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation. Only four studies reported adverse events with no statistically significant differences between groups.

Conclusions: In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.

Signs and Symptoms of Hypothyroidism

HIS FIRM CAP
- Hypoventilation
- Intolerance to cold
- Slow HR
- Fatigue
- Impotence
- Renal impairment
- Menorrhagia/amenorrhea
- Constipation
- Anemia
- Paresthesia
Clinical Features

Table 20. Clinical Features of Hypothyroidism

<table>
<thead>
<tr>
<th>General</th>
<th>Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia, hyperhomocysteinemia, myxedema heart</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Decreased exercise capacity, hypoventilation secondary to weak muscles, decreased pulmonary responses to hypoxia, sleep apnea due to macroglossia</td>
</tr>
<tr>
<td>GI</td>
<td>Weight gain despite poor appetite, constipation</td>
</tr>
<tr>
<td>Neurology</td>
<td>Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes (“hung reflexes”), carpal tunnel syndrome, asymptomatic increase in CK, seizures</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Puffiness of face, periorbital edema, cool and pale, dry and rough skin, hair dry and coarse, eyebrows thinned (lateral 1/3), discoloration (carotenemia)</td>
</tr>
<tr>
<td>Hematology</td>
<td>Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto’s thyroiditis</td>
</tr>
</tbody>
</table>

Treatment

- L-thyroxine (dose range: 0.05-0.2 mg PO OD ~1.6 μg/kg/d)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up TSH with patient annually
- secondary/tertiary hypothyroidism
  - monitor via measurement of free T₄ (TSH is unreliable in this setting)

CONGENITAL HYPOTHYROIDISM

- see Pediatrics, P29

Hashimoto’s Thyroiditis

- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a rubbery goiter and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from the start
  - associated with thyroid lymphoma

Etiology and Pathophysiology

- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na⁺/I symporter

Risk Factors

- female gender
- genetic susceptibility: increased frequency in patients with Down’s syndrome, Turner’s syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake
- stress and infection

Investigations

- high TSH, low T₄ (not necessary to measure T₃ as it will be low as well)
- presence of thyroid peroxidase and thyroglobulin antibodies in serum

Treatment

- if hypothyroid, replace with L-thyroxine (analog of T₄)
Myxedema Coma

Definition
- severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – medical emergency!
- rare, high level of mortality when it occurs (up to 60%, despite therapy)

Clinical Features
- hallmark symptoms of decreased mental status and hypothermia; hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized edema often present

Investigations
- decreased T₄, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment
- aggressive treatment required
- ABCs: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated; also consider T₃ therapy
- supportive measures: mechanical ventilation, fluids, vasopressor drugs, passive rewarming, IV dextrose
- monitor for arrhythmia

Sick Euthyroid Syndrome

Definition
- changes in circulating thyroid hormones amongst patients with serious illness, trauma, or stress
- not due to intrinsic thyroid or pituitary disease
- initially low free T₃ may be followed by low TSH and if severe illness low free T₄
- with recovery of illness, TSH may overshoot and become transiently high

Pathophysiology
- abnormalities in SES include alterations in
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
  - thyroid function itself
  - peripheral conversion of T₄ to T₃

Labs
- initially decreased free T₃ followed by decreased TSH and finally decreased free T₄

Treatment
- treat the underlying disease; thyroid hormone replacement worsens outcomes
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

Non-Toxic Goiter

Definition
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

Pathophysiology
- the appearance of a goiter is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages: goiter is usually diffuse
  - later stages: multinodular non-toxic goiter with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

Etiology
- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone
Treatment
• remove goitrogens
• radiiodine therapy (need very high doses, low iodine uptake, used as last resort)
• suppression with L-thyroxine (rarely done)
• surgery may be necessary for severe compressive symptoms

Complications
• compression of neck structures causing stridor, dysphagia, pain, and hoarseness
• multinodular goiter may become autonomous leading to toxic multinodular goiter and hyperthyroidism

Thyroid Nodules
Definition
• clearly defined discrete mass, separated from the thyroid parenchyma
• palpable nodules are found in approximately 5% of the population
• M:F = 1:4

Etiology
• benign tumors (e.g. colloid nodule, follicular adenoma)
• thyroid malignancy
• hyperplastic area in a multinodular goiter
• cyst: true thyroid cyst, area of cystic degeneration in a multinodular goiter

Investigations

Figure 8. Approach to the evaluation of a thyroid nodule
Adapted from Dr. J Goguen, University of Toronto, MMMD 2013

Thyroid Malignancies
• see Otolaryngology, OT38

Adrenal Cortex

Adrenocorticotropic Hormone
• a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400; trough: 1800-2400)
• secretion regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)
• stimulates growth of adrenal cortex and release of glucocorticoids, androgens and, to a limited extent, mineralocorticoids
• some melanocyte stimulating activity

Adrenocortical Hormones
Aldosterone
• a mineralocorticoid which regulates extracellular fluid (ECF) volume through Na⁺ (and Cl⁻) retention and K⁺ (and H⁺) excretion (stimulates distal tubule Na⁺/K⁺ ATPase)
• regulated by the renin-angiotensin-aldosterone system (Figure 11)
• negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone → volume expansion) and short loop (angiotensin II → peripheral vasoconstriction)
Cortisol
- a glucocorticoid, regulated by the HPA axis
- involved in regulation of metabolism; counteracts the effects of insulin
- support blood pressure, vasomotor tone
- also involved in regulation of behavior and immunosuppression

Table 21. Physiological Effects of Glucocorticoids

<table>
<thead>
<tr>
<th>Stimulatory Effects</th>
<th>Inhibitory Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulate hepatic glucose production (gluconeogenesis)</td>
<td>Inhibit bone formation; stimulate bone resorption</td>
</tr>
<tr>
<td>Increase insulin resistance in peripheral tissues</td>
<td>Inhibit fibroblasts, causing collagen and connective tissue loss</td>
</tr>
<tr>
<td>Increase protein catabolism</td>
<td>Suppress inflammation; impair cell-mediated immunity</td>
</tr>
<tr>
<td>Stimulate leukocytosis and lymphopenia</td>
<td>Inhibit growth hormone axis</td>
</tr>
<tr>
<td>Increase cardiac output, vascular tone, Na⁺ retention</td>
<td>Inhibit reproductive axis</td>
</tr>
<tr>
<td>Increase PTH release, urine calcium excretion</td>
<td>Inhibit vitamin D₃ and inhibit calcium uptake</td>
</tr>
</tbody>
</table>

Androgens
- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are dehydroepiandrosterone (DHEA), androstenedione, and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age
Adrenocortical Functional Workup

**STIMULATION TEST**
- **purpose:** diagnosis of hormone deficiencies
- **method:** measure target hormone after stimulation with tropic (pituitary) hormone

1. **Tests of Glucocorticoid Reserve**
   - **Cosyntropin (ACTH analogue) Stimulation Test**
     - give 1 µg or 250 µg cosyntropin IV, then measure plasma cortisol levels at time 0, 30, and 60 min
     - physiologic response: stimulated plasma cortisol of >18 µg/dL (500 nmol/L)
     - inappropriate response: inability to stimulate increased plasma cortisol
   - insulin tolerance test used to diagnose secondary or tertiary hypoadrenalism (see Pituitary Gland, E16)

2. **SUPPRESSION TESTS**
   - **purpose:** diagnosis of hormone hypersecretion
   - **method:** measure target hormone after suppression of its tropic (pituitary) hormone

1. **Tests of Pituitary-Adrenal Suppressibility**
   - **Dexamethasone (DXM) Suppression Test**
     - **principle:** DXM suppresses pituitary ACTH → plasma cortisol should be lowered if HPA axis is normal
     - **Screening Test:** Overnight DXM Suppression Test
       - oral administration of 1 mg DXM at midnight → measure plasma cortisol levels the following day at 8 am
       - physiologic response: plasma cortisol <1.8 µg/dL (50 nmol/L), with 1.8-5.0 µg/dL (50-140 nmol/L) being a “grey zone” (cannot be certain if normal or not)
       - inappropriate response: failure to suppress plasma cortisol
       - <20% false positive results due to obesity, depression, alcohol, other medications
     - **Confirmatory Test:** Other testing is used to confirm the diagnosis, such as:
       - midnight salivary cortisol (if available), shows lack of diurnal variation
       - inappropriate response: remains high (normally will be low at midnight)

2. **Tests of Mineralocorticoid Suppressibility**
   - **principle:** expansion of extracellular fluid volume (ECFV) → plasma aldosterone should be lowered if HPA axis were normal
   - **ECFV Expansion with Normal Saline (NS)**
     - IV infusion of 500 mL/h of NS for 4 h → then measure plasma aldosterone levels
     - plasma aldosterone >10 ng/dL (>277 pmol/L) is consistent with primary hyperaldosteronism, <5 ng/dL (<140 pmol/L) is normal
     - inappropriate response: failure to suppress plasma aldosterone
Mineralocorticoid Excess Syndromes

**Definition**
- primary hyperaldosteronism (PH): excess aldosterone production (intra-adrenal cause)
- secondary hyperaldosteronism (SH): aldosterone production in response to excess RAAS (extra-adrenal cause)

**Etiology**
- primary hyperaldosteronism
  - aldosterone-producing adrenal adenoma (Conn’s syndrome)
  - bilateral or idiopathic adrenal hyperplasia
  - glucocorticoid-remediable aldosteronism
  - aldosterone-producing adrenocortical carcinoma
  - unilateral adrenal hyperplasia
- secondary hyperaldosteronism

**Clinical Features**
- HTN
- hypokalemia (may have mild hypernatremia), metabolic alkalosis
- normal K+, low Na+ in SH (low effective circulating volume leads to ↑ ADH release) → edema
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, MI
- fatigue, weakness, paresthesia, headache; severe cases with tetany, intermittent paralysis

**Diagnosis**
- investigate plasma aldosterone to renin ratio in patients with HTN and hypokalemia
- confirmatory testing for PH: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECFV expansion)
- imaging: CT adrenal glands

**Table 22. Diagnostic Tests in Hyperaldosteronism**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary Hyperaldosteronism</th>
<th>Secondary Hyperaldosteronism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma aldosterone to renin ratio (PAC/PRA)</td>
<td>Elevated (↑ ald, ↓ renin)</td>
<td>Normal (↑ ald, ↓ renin)</td>
</tr>
<tr>
<td>Salt loading test:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A) Oral test:</td>
<td>↑ urine aldosterone</td>
<td>Not performed if normal PAC/PRA</td>
</tr>
<tr>
<td>B) IV saline test:</td>
<td>↑ plasma aldosterone</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**
- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause
Cushing’s Syndrome

Definition
• results from chronic glucocorticoid excess (endogenous or exogenous sources)

Etiology
• ACTH-dependent (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
  ▪ ACTH-secreting pituitary adenoma (Cushing’s disease; 80% of ACTH-dependent)
  ▪ ectopic ACTH-secreting tumor (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma, or medullary thyroid tumors)
• ACTH-independent (15%)
  ▪ long-term use of exogenous glucocorticoids
  ▪ primary adrenocortical tumors: adenoma and carcinoma (uncommon)
  ▪ bilateral adrenal nodular hyperplasia

Clinical Features
• symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism, and acne (ACTH dependent)
• signs: central obesity, round face, supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, HTN, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism if ACTH-dependent

Figure 14. Hypercortisolism: algorithm for diagnosis

Treatment
• adrenal
  ▪ adenoma: unilateral adrenalectomy (curative)
  ▪ carcinoma: adjunctive chemotherapy often not useful (frequent metastases, poor prognosis)
  ▪ medical treatment: mitotane, ketoconazole to reduce cortisol
• pituitary
  ▪ trans-sphenoidal resection, with glucocorticoid supplement post-operatively
  ▪ ectopic ACTH tumor (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis)
    ▪ surgical resection, if possible; chemotherapy/radiation for primary tumor
    ▪ agents blocking adrenal steroid synthesis: metyrapone or ketoconazole

Congenital Adrenal Hyperplasia

• see Pediatrics, P30
Hyperandrogenism

Definition

• state of having excessive secretion of androgens (DHEA, DHEA sulfate, testosterone)

Etiology and Pathophysiology

Table 23. Etiology of Hyperandrogenism

<table>
<thead>
<tr>
<th>Constitutional/Familial</th>
<th>Family history, predisposing ethnic background</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Premature adrenarche</td>
</tr>
<tr>
<td>Medications</td>
<td>Anabolic steroids, ACTH, androgens, progestational agents</td>
</tr>
<tr>
<td>Androgen-Mediated</td>
<td></td>
</tr>
<tr>
<td>Ovarian</td>
<td>PCOS</td>
</tr>
<tr>
<td></td>
<td>Ovarian hyperthecosis</td>
</tr>
<tr>
<td></td>
<td>Theca cell tumors</td>
</tr>
<tr>
<td></td>
<td>Pregnancy: placental sulfatase/aromatase deficiency</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Congenital adrenal hyperplasia (CAH, late-onset CAH)</td>
</tr>
<tr>
<td></td>
<td>Tumors (adenoma, carcinoma)</td>
</tr>
<tr>
<td>Pituitary</td>
<td>Cushing’s disease – high ACTH</td>
</tr>
<tr>
<td></td>
<td>Hyperprolactinemia</td>
</tr>
</tbody>
</table>

Clinical Features

Females

• hirsutism
  ▪ male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  ▪ Ferriman-Gallwey scoring system is used to quantify severity of hirsutism
• virilization
  ▪ masculinization: hirsutism, temporal balding, clitoral enlargement, deepening of voice, acne
  ▪ increase in musculature
• defeminization
  ▪ loss of female secondary sex characteristics (i.e. amenorrhea, ↓ breast size, infertility)

Males

• minimal effects on hair, muscle mass, etc.
• inhibition of gonadotropin secretion may cause reduction in: testicular size, testicular testosterone production, and spermatogenesis

Investigations

• testosterone, DHEA-S as a measure of adrenal androgen production
• LH/FSH (commonly in PCOS >2.5)
• 17-OH progesterone, elevated in CAH due to 21-OH deficiency
• for virilization: CT/MRI of adrenals and ovaries (identify tumors)
• if PCOS, check blood glucose, lipids, 75 g OGTT

Treatment

• discontinue causative medications
  ▪ antiandrogens, e.g. spironolactone
• oral contraceptives (e.g. cyproterone acetate – blocks androgen receptor; found in Diane 35°)
• surgical resection of tumor
• low dose glucocorticoid ± mineralocorticoid if CAH suspected
• treat specific causative disorders, e.g. tumors, Cushing’s, etc.
• cosmetic therapy (laser, electrolysis)

Conditions that do NOT Represent True Hirsutism

• Androgen-independent hair (e.g. lanugo hair)
• Drug-induced hypertrichosis (e.g. phenytoin, diazoxide, cyclosporine, minoxidil)
• Topical steroid use
Adrenocortical Insufficiency

Definition
- a state of inadequate cortisol and aldosterone production by the adrenal glands

Etiology

PRIMARY (ADDISON’S DISEASE)

<table>
<thead>
<tr>
<th>Autoimmune (70-90%)</th>
<th>Isolated adrenal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Polyglandular autoimmune syndrome type I and II</td>
</tr>
<tr>
<td></td>
<td>Antibodies often directed against adrenal enzymes and 3 cortical zones</td>
</tr>
</tbody>
</table>

Infection
- TB (7-20%) (most common in developing world)
- Fungal: histoplasmosis, paracoccidioidomycosis
- HIV, CMV
- Syphilis
- African trypanosomiasis

Infiltrative
- Metastatic cancer (lung > stomach > esophagus > colon > breast; lymphoma)
- Sarcoidosis, amyloidosis, hemochromatosis

Vascular
- Bilateral adrenal hemorrhage
- Sepsis (meningococcal, Pseudomonas)
- Coagulopathy in adults or Waterhouse-Friderichsen syndrome in children
- Thrombosis, embolism, adrenal infarction

Drugs
- Inhibit cortisol: ketoconazole, megestrol acetate
- Increase cortisol metabolism: rifampin, phenytoin, barbiturates, heparin, coumadin

Others
- Adrenoleukodystrophy
- Congenital adrenal hypoplasia (impaired steroidogenesis)
- Familial glucocorticoid deficiency or resistance

SECONDARY ADRENOCORTICAL INSUFFICIENCY
- inadequate pituitary ACTH secretion
- multiple etiologies (see Hypopituitarism, E20), including withdrawal of exogenous steroids

Clinical Features

<table>
<thead>
<tr>
<th>Primary AI (Addison’s or Acute AI)</th>
<th>Secondary AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and Mucosa</td>
<td></td>
</tr>
<tr>
<td>Dark (palmar crease, extensor surface)</td>
<td>Pale</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Normal or Low</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Associated Diseases</td>
<td></td>
</tr>
<tr>
<td>Primary hypothyroidism, type 1 DM, vitiligo, neurological deficits</td>
<td>Central hypogonadism or hypothyroidism, growth hormone deficiency, DI, headaches, visual abnormalities</td>
</tr>
<tr>
<td>Associated Symptoms</td>
<td></td>
</tr>
<tr>
<td>Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia</td>
<td>Same except: NO salt craving</td>
</tr>
<tr>
<td>GI: N/V; abdominal pain, diarhea</td>
<td>GI less common</td>
</tr>
<tr>
<td>Diagnostic Test</td>
<td></td>
</tr>
<tr>
<td>Cosyntropin Stimulation Test</td>
<td>Insulin tolerance test</td>
</tr>
<tr>
<td>High morning plasma ACTH</td>
<td>Cosyntropin Stimulation Test</td>
</tr>
</tbody>
</table>

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

Treatment
- acute condition – can be life-threatening
  - IV NS in large volumes (2-3 L); add D5W if hypoglycemic from adrenal insufficiency
  - hydrocortisone 50-100 mg IV q6-8h for 24h, then gradual tapering
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-20 mg total daily dose, in 2-3 divided doses, highest dose in the AM
  - Florinef® (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
- major stress (e.g. surgery, trauma) requires 150-300 hydrocortisone IV daily divided into 3 doses
- medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection
Adrenal Medulla

Catecholamine Metabolism

- Catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine).
- Broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine.

Pheochromocytoma

Definition

- Rare catecholamine secreting tumor derived from chromaffin cells of the sympathetic system.
- Most commonly a single tumor of adrenal medulla.
- Rare cause of HTN (<0.2% of all hypertensives).

Epidemiology

- Most cases sporadic (80%).
- Familial: associated with multiple endocrine neoplasia II (MEN IIA and IIB) (50% penetrance; i.e. 50% of people with the mutation get pheochromocytoma), von Hippel-Lindau (10-20% penetrance), paraganglioma (20% penetrance), or neurofibromatosis type 1 (0.1-5.7% penetrance).

Etiology and Pathophysiology

- Tumors, via unknown mechanism, able to synthesize and release excessive catecholamines.

Clinical Features

- 50% suffer from paroxysmal HTN; the rest have sustained HTN.
- Classic triad: episodic "pounding" headache, palpitations/tachycardia, diaphoresis.
- Other symptoms: tremor, anxiety, chest or abdominal pain, N/V, visual blurring, weight loss, polyuria, polydipsia.
- Other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy.
- Symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods).

Investigations

- Increased catecholamine metabolites (metanephrines) and free catecholamines.
- Plasma metanephrines if available (most sensitive).
- Cut-off values will depend on assay used.

- CT abdomen if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI.

Treatment

- Surgical removal of tumor (curative) with careful pre- and post-operative ICU monitoring.
- Adequate pre-operative preparation.
  - $\alpha$-blockade for BP control: phenoxybenzamine (10-21 d pre-operative), IV phentolamine (perioperative, if required).
  - $\beta$-blockade for HR control once $\alpha$ blocked for a few days.
  - Metyrosine (catecholamine synthesis inhibitor) + phenoxybenzamine or prazosin.
  - Volume restoration with vigorous salt-loading and fluids.
- Rescreen urine 1-3 mo post-operatively.
- Screen urine in first degree relatives; genetic testing in patients <50 yr old.

Disorders of Multiple Endocrine Glands

Multiple Endocrine Neoplasm

- Neoplastic syndromes involving multiple endocrine glands.
- Tumors of neuroectodermal origin.
- Autosomal dominant inheritance with variable penetrance.
- Genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit in MEN II.
  - Early cure and prevention of medullary thyroid cancer.
Table 26. MEN Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissues Involved</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN I</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pituitary</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anterior pituitary adenoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parathyroid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary hyperparathyroid from hyperplasia</td>
<td>Headache, visual field defects. Often non-secreting but may</td>
</tr>
<tr>
<td></td>
<td></td>
<td>secrete GH (acromegaly) and PRL (galectorrhea, erectile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dysfunction, decreased libido, amenorrhea)</td>
</tr>
<tr>
<td></td>
<td>Entero-pancreatic endocrine</td>
<td>Nephrolithiasis, bone abnormalities, MSK complaints,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>symptoms of hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Pancreatic islet cell tumors</td>
<td>Epigastric pain (peptic ulcers and esophagitis)</td>
</tr>
<tr>
<td></td>
<td>Gastrinoma</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Insulinomas</td>
<td>Secretory diarrhea</td>
</tr>
<tr>
<td></td>
<td>Vasoactive intestinal peptide</td>
<td>Rash, anorexia, anemia, diarrhea, glossitis</td>
</tr>
<tr>
<td></td>
<td>VIP-omas</td>
<td>Flushing, diarrhea, bronchospasm</td>
</tr>
<tr>
<td></td>
<td>Glucagonoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carcinoid syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary hyperparathyroid from hyperplasia</td>
<td>Headache, visual field defects. Often non-secreting but may</td>
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<tr>
<td></td>
<td></td>
<td>dysfunction, decreased libido, amenorrhea)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nephrolithiasis, bone abnormalities, MSK complaints,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>symptoms of hypercalcemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epigastric pain (peptic ulcers and esophagitis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Secretory diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash, anorexia, anemia, diarrhea, glossitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flushing, diarrhea, bronchospasm</td>
</tr>
</tbody>
</table>

MEN II (chromosome 10)

1. IIa Sipple’s Syndrome

<table>
<thead>
<tr>
<th>Thyroid (90%)</th>
<th>Medullary thyroid cancer (MTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal medulla (40-50%)</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Parathyroid (10-20%)</td>
</tr>
<tr>
<td>1st parathyroid hyperplasia</td>
<td>Skin</td>
</tr>
<tr>
<td>Cutaneous lichen amyloidosis</td>
<td>Thyroid</td>
</tr>
</tbody>
</table>

MTC without other clinical manifestations of MEN IIa or IIb

2. Familial Medullary Thyroid Ca

<table>
<thead>
<tr>
<th>Thyroid</th>
<th>MTC</th>
</tr>
</thead>
</table>

MTC: most common component, more aggressive and earlier onset than MEN IIa

3. IIb

<table>
<thead>
<tr>
<th>Thyroid</th>
<th>MTC</th>
</tr>
</thead>
</table>

Chronic constipation; megacolon

MRN for thyroid nodules → cytology

Investigations

- MEN I
  - laboratory
    - may consider genetic screening for MEN-1 mutation in index patients
      - if a mutation is identified, screen family members who are at risk
    - gastrinoma: elevated serum gastrin level (>200 ng/mL) after IV injection of secretin
    - insulinoma: reduced fasting blood glucose (hypoglycemia) with elevated insulin and C-peptide levels
    - glucagonoma: elevated blood glucose and glucagon levels
    - pituitary tumors: assess GH, IGF-1 and prolactin levels (for over-production), TSH, free T4, 8 AM cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumor)
    - hyperparathyroidism: serum Ca²⁺ and albumin, PTH levels; bone density scan (DEXA)
  - imaging
    - MRI for pituitary tumors, gastrinoma, insulinoma

- MEN II
  - laboratory
    - genetic screening for RET mutations in all index patients
      - if a mutation is identified, screen family members who are at risk
    - calcitonin levels (MTC); urine catecholamines and metanephrines (pheochromocytoma); serum Ca²⁺, albumin and PTH levels (hyperparathyroidism)
    - pentagastrin ± calcium stimulation test if calcitonin level is within reference range
    - FNA for thyroid nodules → cytology
  - imaging
    - CT or MRI of adrenal glands, metaiodobenzylguanidine (MIBG) scan for pheochromocytoma
    - octreoscan and/or radionuclide scanning for determining the extent of metastasis

Treatment

- MEN I
  - medical
    - proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma
    - cabergoline or other dopamine agonists to suppress prolactin secretion
    - somatostatin for symptomatic carcinoid tumors
  - surgery for hyperparathyroidism, insulinoma, glucagonoma, pituitary tumors (if medical treatment fails for the latter)
    - trans-sphenoidal approach with prn external radiation

- MEN II
  - surgery for MTC
  - radiotherapy for pheochromocytoma

MEN I – Wermer’s Syndrome Affects the 3 Ps

Pituitary
Parathyroid
Pancreas
• MEN II
  • surgery for MEN IIA with pre-operative medical therapy
    • prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer
    • α-blocker for at least 10-21 d for pheochromocytoma pre-operatively
    • hydration, calcitonin, IV bisphosphonates for hypercalcemia

**Calcium Homeostasis**

- normal total serum Ca\(^{2+}\): 8.5-10.5 mg/dL (2.2-2.6 mmol/L)
- ionic/free Ca\(^{2+}\) levels: 4.6-5.25 mg/dL (1.15-1.31 mmol/L)
- serum Ca\(^{2+}\) is about 50% protein bound (mostly albumin)
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D
- actions mainly on three organs: GI tract, bone, and kidney

### Table 27. Major Regulators in Calcium Homeostasis

<table>
<thead>
<tr>
<th>Major Regulators</th>
<th>Source</th>
<th>Regulation</th>
<th>Not Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>Parathyroid glands</td>
<td>Stimulated by low serum Ca(^{2+}) and high serum PO(_4^{3-}); inhibited by chronic low serum Mg(^{2+}), high serum Ca(^{2+}), and calcitriol</td>
<td>↑ Ca(^{2+}) ↓ PO(_4^{3-})</td>
</tr>
<tr>
<td>Calcitriol ((1,25-\text{OH})_2\text{D}_3)</td>
<td>Dietary intake</td>
<td>Renal calcitriol production is stimulated by low serum PO(_4^{3-}) and PTH; inhibited by high serum PO(_4^{3-}) and calcitriol in negative feedback</td>
<td>↑ Ca(^{2+}) ↓ PO(_4^{3-})</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Thyroid C cells</td>
<td>Stimulated by pentagastrin (GI hormone) and high serum Ca(^{2+}); inhibited by low serum Ca(^{2+}) (in pharmacologic doses)</td>
<td>↓ Ca(^{2+}) ↓ PO(_4^{3-})</td>
</tr>
<tr>
<td>Mg(^{2+})</td>
<td>Major intracellular divalent cation</td>
<td>See section on Magnesium (E42)</td>
<td>Cofactor for PTH secretion</td>
</tr>
<tr>
<td>PO(_4^{3-})</td>
<td>Intracellular anion found in all tissues</td>
<td>See section on Phosphate (E41)</td>
<td>↓ Ca(^{2+})</td>
</tr>
</tbody>
</table>

### Figure 15. Parathyroid hormone (PTH) regulation

**Pseudohypercalcemia:** increased protein binding leading to an elevation in serum total Ca\(^{2+}\) without a rise in the ionized/free form, e.g. hyperalbuminemia from severe dehydration

**Primary Hyperparathyroidism:**
Increased PTH secretion commonly due to parathyroid adenoma, lithium therapy; less often parathyroid carcinoma or parathyroid hyperplasia

**Secondary Hyperparathyroidism:**
Partial resistance to PTH action leads to parathyroid gland hyperplasia and increased PTH secretion, often in patients with renal failure and osteomalacia (due to low or low normal serum calcium levels)

**Tertiary Hyperparathyroidism:**
Irreversible clonal outgrowth of parathyroid glands, usually in long-standing inadequately treated chronic renal failure on dialysis

**Primary Hyperparathyroidism** is the most common cause of hypercalcemia in healthy outpatients. Most commonly related to a solitary adenoma or less commonly multiple gland hyperplasia. Surgical excision acts as a definitive treatment and is recommended for patients who are symptomatic. For mild asymptomatic disease medical surveillance may be appropriate with annual serum calcium, creatinine, and BMD.

For asymptomatic patients surgery is recommended for those who meet ≥1 of the following criteria:
- Serum calcium concentration more than 1.0 mg/dL (0.25 mmol/L) above the upper limit of normal
- Creatinine clearance <60 mL/min
- BMD T-score <−2.5 at hip, spine, or distal radius, and/or previous fragility fracture
- Age <50 yr
**Hypercalcemia**

**Definition**
- total corrected serum Ca²⁺ >10.5 mg/dL (2.6 mmol/L) OR ionized Ca²⁺ >5.4 mg/dL (1.35 mmol/L)

**Approach to Hypercalcemia**
1. Is the patient hypercalcemic? (correct for albumin – see sidebar)
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low? If phosphate is high/normal is the level of vitamin D metabolites high or low?

**Figure 16. Differential diagnosis of hypercalcemia**

**Clinical Features**
- symptoms depend on the absolute Ca²⁺ value and the rate of its rise (may be asymptomatic)

**Table 28. Symptoms of Hypercalcemia**

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>GI</th>
<th>Renal</th>
<th>Rheumatological</th>
<th>MSK</th>
<th>Psychiatric</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>Anorexia</td>
<td>Vomiting</td>
<td>Polyuria</td>
<td>Gout</td>
<td>Increased alertness</td>
<td>Hypertonia</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>Constipation</td>
<td>Polydipsia</td>
<td>Chondrocalcinosis</td>
<td>Weakness</td>
<td>Anxiety</td>
<td>Hyporeflexia</td>
</tr>
<tr>
<td>Short QT</td>
<td>Nausea</td>
<td>Nephrolithiasis (stones)</td>
<td>Renal failure (irreversible)</td>
<td>Bone pain (bones)</td>
<td>Depression</td>
<td>Myopathy</td>
</tr>
<tr>
<td>Deposition of Ca²⁺ on valves, coronary arteries, myocardial fibers</td>
<td>PUD</td>
<td>Renal failure (irreversible)</td>
<td>Gout</td>
<td>Weakness</td>
<td>Organic brain syndromes</td>
<td>Paresis</td>
</tr>
</tbody>
</table>

**Treatment**
- treatment depends on the Ca²⁺ level and the symptoms
- treat acute, symptomatic hypercalcemia aggressively

**Corrected Ca²⁺ (mmol/L) = measured Ca²⁺ + 0.02 (40 – albumin)**
- For every decrease in albumin by 10, increase in Ca²⁺ by 0.2
- Benign (less likely malignant): Ca²⁺ <2.75 mmol/L (11 mg/dL)
- Pathologic (more likely malignant): Ca²⁺ >3.25 mmol/L (13 mg/dL)
Hypocalcemia

Definition
- total corrected serum Ca\(^{2+}\) <8.5 mg/dL (2.2 mmol/L)

Table 30. Clinical Features of Hypocalcemia

<table>
<thead>
<tr>
<th>Acute Hypocalcemia</th>
<th>Chronic Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson’s, dystonia, hemiballismus, papilledema, pseudotumor cerebri</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>CVS: prolonged QT interval → Torsades de pointes (ventricular tachycardia)</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>GI: steatorrhea</td>
</tr>
<tr>
<td>Chvostek’s sign</td>
<td>ENDO: impaired insulin release</td>
</tr>
<tr>
<td>Trousseau’s sign</td>
<td>SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition</td>
</tr>
<tr>
<td>ECG changes</td>
<td>OCULAR: cataracts</td>
</tr>
<tr>
<td>Delirium</td>
<td>MSK: generalized muscle weakness and wasting</td>
</tr>
<tr>
<td>Psychiatric Sx:</td>
<td>emotional instability, anxiety, and depression</td>
</tr>
</tbody>
</table>

Approach to Hypocalcemia
1. Is the patient hypocalcemic?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?
4. Is the Mg\(^{2+}\) level low?

Approach to Treatment
- correct underlying disorder
- mild/asymptomatic (ionized Ca\(^{2+}\) >3.2 mg/dL, 0.8 mmol/L)
  - treat by increasing dietary Ca\(^{2+}\) by 1000 mg/d
  - calcitriol 0.25 µg/d
- acute/asymptomatic hypocalcemia (ionized Ca\(^{2+}\) <2.8 mg/dL, 0.7 mmol/L)
  - immediate treatment required
  - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion if necessary
  - goal is to raise Ca\(^{2+}\) to low normal range (8.0-8.4 mg/dL, 2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH secretion
- if PTH recovery not expected, requires long-term therapy with calcitriol and calcium
- do not correct hypocalcemia if asymptomatic and suspected to be transient
Hyperphosphatemia

Definition
- serum phosphate >4.1 mg/dL (1.45 mmol/L)

Table 31. Etiology of Hyperphosphatemia

<table>
<thead>
<tr>
<th>Increased Phosphate Load</th>
<th>Reduced Renal Clearance</th>
<th>Pseudohyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI intake (rectal enema, GI bleeding)</td>
<td>Acute/chronic renal failure</td>
<td>Hyperglobulinemia</td>
</tr>
<tr>
<td>IV phosphate load (K-Phos®, blood transfusion)</td>
<td>Hyperparathyroidism</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Endogenous phosphate (tumor lysis syndrome, rhabdomyolysis, hemolysis, lactic and ketoacidosis)</td>
<td>Acromegaly</td>
<td>Hyperbilirubinemia</td>
</tr>
</tbody>
</table>

Clinical Features
- non-specific, include ectopic calcification, renal osteodystrophy

Treatment
- acute: hemodialysis if symptomatic
- chronic: low PO₄³⁻ diet, phosphate binders (e.g. CaCO₃ with meals)

Hypophosphatemia

Definition
- serum phosphate <2.4 mg/dL (0.85 mmol/L)

Table 32. Etiology of Hypophosphatemia

<table>
<thead>
<tr>
<th>Inadequate Intake</th>
<th>Renal Losses</th>
<th>Excessive Skeletal Mineralization</th>
<th>Shift into ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starvation</td>
<td>Hyperparathyroidism</td>
<td>Osteoblastic metastases</td>
<td>Recovery from metabolic acidosis</td>
</tr>
<tr>
<td>Malabsorption (diarrhea, steatorrhea)</td>
<td>Diuretics</td>
<td>Post parathyroidectomy (referred to as ‘hungry bone syndrome’)</td>
<td>Respiratory alkalosis</td>
</tr>
<tr>
<td>Antacid use</td>
<td>X-linked or AD</td>
<td>Fanciù syndrome</td>
<td>Starvation refeeding (stimulated by insulin)</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>Hypophosphatemic rickets</td>
<td>Multiple myeloma</td>
<td></td>
</tr>
</tbody>
</table>

Symptoms usually present when phosphate <1.0 mg/dL (0.32 mmol/L)
Treat asymptomatic patients if phosphate <2.0 mg/dL (0.64 mmol/L)
Clinical Features
• non-specific (CHF, coma, hypotension, weakness, defective clotting)

Treatment
• treat underlying cause
  ▪ Oral PO₄³⁻: 2-4 g/d divided bid-qid (start at 1 g/d to minimize diarrhea)
  ▪ IV PO₄³⁻: only for severely symptomatic patients or inability to tolerate oral therapy

Hypermagnesemia

Definition
• serum magnesium >2.1 mg/dL (0.85 mmol/L)

Etiology
• AKI/CRF
• Mg²⁺-containing antacids or enemas
• IV administration of large doses of MgSO₄ (e.g., for preeclampsia; see Obstetrics, OB16)

Clinical Features
• drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest

Treatment
• discontinue Mg²⁺-containing products
• IV calcium (Mg²⁺-antagonist) for acute reversal of magnesium toxicity
• dialysis if renal failure

Hypomagnesemia

Definition
• serum magnesium <1.7 mg/dL (0.70 mmol/L)

Etiology
• GI losses
  ▪ starvation/malabsorption
  ▪ vomiting/diarrhea
  ▪ alcoholism
  ▪ acute pancreatitis
• excess renal loss
  ▪ 2° hyperaldosteronism due to cirrhosis and CHF
  ▪ hyperglycemia
  ▪ hypokalemia
  ▪ hypercalcemia
  ▪ loop and thiazide-type diuretics
  ▪ nephrotoxic medications
  ▪ proton-pump inhibitors

Clinical Features
• seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities), and arrhythmias including Torsades de pointes

Treatment
• treat underlying cause
• Mg²⁺ IM/IV; cellular uptake of Mg²⁺ is slow, therefore repletion requires sustained correction
• discontinue diuretics
  ▪ in patients requiring diuretics, use a K⁺-sparing diuretic to minimize magnesuria

Metabolic Bone Disease

Osteoporosis

Definition
• a condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture
• bone mineral density (BMD) ≥2.5 standard deviations below the peak bone mass for young adults (i.e., T-score ≤−2.5)
• osteopenia: BMD with T-score between −1.0 and −2.5

ETIOLOGY AND PATHOPHYSIOLOGY

Primary Osteoporosis
• primary type 1: most common in post-menopausal women, due to decline in estrogen, worsens with age
• primary type 2: occurs after age 75, seen in females and males at 2:1 ratio, possibly due to zinc deficiency

You will be unable to correct hypokalemia or hypocalcemia without first supplementing magnesium if patient hypomagnesemic

Online Clinical Tools
CAROC.pdf
FRAX
www.shef.ac.uk/FRAX/tool.aspx
Secondary Osteoporosis
- gastrointestinal diseases
  - gastrectomy
  - malabsorption (e.g., celiac disease)
  - chronic liver disease
- bone marrow disorders
  - multiple myeloma
  - lymphoma
  - leukemia
- endocrinopathies
  - Cushing's syndrome
  - hyperparathyroidism
  - hyperthyroidism
  - premature menopause
  - DM
- malignancy
  - secondary to chemotherapy
  - myeloma

Clinical Features
- commonly asymptomatic
- height loss due to collapsed vertebrae
- fractures: most commonly in hip, vertebrae, humerus, and wrist
- fragility fractures: fracture with fall from standing height
- Paget's disease: weakening of subchondral plates and expansion of intervertebral discs
- x-ray: vertebral compression and crush fractures, wedge fractures, "codfishing" sign
- pain, especially backache, associated with fractures

Approach to Osteoporosis
1. Assess risk factors for osteoporosis on history and physical
2. Decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA)
   - men
     - 10 yr fracture risk 10-20%
     - Medium Risk
     - 10 yr fracture risk <10%
     - Low Risk
     - 10 yr fracture risk >20%
     - OR
     - Prior fragility fracture of hip or spine
     - OR
     - More than one fragility fracture
   - women ≥65 yr or younger if presence of risk factors (Table 33)
   - and women ≥65 yr or younger if presence of risk factors (Table 33)
3. Initial investigations
   - assess risk factors for osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
   - also consider serum and urine protein electrophoresis, celiac workup, and 24 h urinary Ca
   - and excretion to rule out additional secondary causes
   - 25-OH-Vitamin D level should only be measured after 3-4 mo of adequate supplementation and should not be repeated if an optimal level ≥75 nmol/L is achieved
   - lateral thoracic and lumbar x-ray if clinical evidence of vertebral fracture
4. Assess 10 yr fracture risk by combining BMD result and risk factors (only if ≥50 yr)
   - 1) WHO Fracture Risk Assessment Tool (FRAX)
   - 2) Canadian Association of Radiologists and Osteoporosis Canada Risk Assessment Tool (CAROC)
   - approach to management guided by 10 yr risk stratification into low, medium, high risk
5. For all patients being assessed for osteoporosis, encourage appropriate lifestyle changes
   (see Table 35)

Table 33. Osteoporosis Risk Stratification

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>10 yr Fracture Risk</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Risk</strong></td>
<td>&lt;10%</td>
<td>Unlikely to benefit from pharmacotherapy; encourage lifestyle changes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reassess risk in 5 yr</td>
</tr>
<tr>
<td><strong>Medium Risk</strong></td>
<td>10-20%</td>
<td>Discuss patient preference for management and consider additional risk factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factors that warrant consideration for pharmacological therapy:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Previous wrist fracture in individuals ≥65 or with T-score ≤2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lumbar spine T-score much lower than femoral neck T-score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rapid bone loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Men receiving androgen-deprivation therapy for prostate cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Women receiving aromatase-inhibitor therapy for breast cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurrent falls (defined as falling 2 or more times in the past 12 mo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other disorders strongly associated with osteoporosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Repeat BMD and reassess risk every 1-3 yr initially</td>
</tr>
<tr>
<td><strong>High Risk</strong></td>
<td>&gt;20%</td>
<td>Start pharmacotherapy</td>
</tr>
<tr>
<td>Prior fragility fracture of hip or spine</td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>More than one fragility fracture</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 34. Indications for BMD Testing

<table>
<thead>
<tr>
<th>Older Adults (age ≥50 yr)</th>
<th>Younger Adults (age &lt;50 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women and men age ≥65 yr</td>
<td>Fragility fracture</td>
</tr>
<tr>
<td>Menopausal women, and men aged 50-64 yr with clinical risk factors for fracture:</td>
<td>• Prolonged glucocorticoid use</td>
</tr>
<tr>
<td>• Fracture fracture after age 40</td>
<td>• Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy)</td>
</tr>
<tr>
<td>• Prolonged glucocorticoid use</td>
<td>• Hypogonadism or premature menopause</td>
</tr>
<tr>
<td>• Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy)</td>
<td>• Malabsorption syndrome</td>
</tr>
<tr>
<td>• Parental hip fracture</td>
<td>• Primary hyperparathyroidism</td>
</tr>
<tr>
<td>• Vertebral fracture or osteopenia identified on x-ray</td>
<td>• Other disorders strongly associated with rapid bone loss and/or fracture</td>
</tr>
<tr>
<td>• Current smoking</td>
<td>Effect on uterus and breast</td>
</tr>
<tr>
<td>• High alcohol intake</td>
<td>Effect on bone but antagonistic</td>
</tr>
<tr>
<td>• Low body weight (&lt;60 kg) or major weight loss (&gt;10% of weight at age 25 yr)</td>
<td>SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast</td>
</tr>
<tr>
<td>• Rheumatoid arthritis</td>
<td>• +ve: Prevents osteoporotic fracture, decreases breast cancer risk</td>
</tr>
<tr>
<td></td>
<td>• -ve: Increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps</td>
</tr>
<tr>
<td></td>
<td>• Combined estrogen/progesterin prevents hip, vertebral, total fracture</td>
</tr>
<tr>
<td></td>
<td>• Increased risks of breast cancer, cardiovascular events, and DVT/PE</td>
</tr>
</tbody>
</table>

Treatment of Osteoporosis

Table 35. Treatment of Osteoporosis in Women and Men

<table>
<thead>
<tr>
<th>Treatment for Both Men and Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lifestyle</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Drug Therapy</strong></td>
</tr>
<tr>
<td><strong>Bisphosphonate: inhibitors of osteoclast binding</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>RANKL Inhibitors</strong></td>
</tr>
<tr>
<td><strong>Parathyroid Hormone</strong></td>
</tr>
<tr>
<td><strong>Calcitoni (2nd line): osteoclast receptor binding</strong></td>
</tr>
</tbody>
</table>

Table 36. Indications for BMD Testing

<table>
<thead>
<tr>
<th>Negative Test</th>
<th>Positive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall-Occiput Distance &gt;0 cm</td>
<td>Rib-Pelvis Distance ≥2 fingerbreadths</td>
</tr>
</tbody>
</table>

Figure 18. Physical examination test
Osteomalacia and Rickets

- **Rickets**: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *prior* to epiphyseal closure (in childhood)
- **Osteomalacia**: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue *after* epiphyseal closure (in adulthood)

**Etiology and Pathophysiology**

**Vitamin D Deficiency**
- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy
- loss of vitamin D binding protein
  - nephrotic syndrome
- defective 1-a-25 hydroxylation
  - hypoparathyroidism
  - renal failure
  - pathophysiology: leads to secondary hyperparathyroidism and hypophosphatemia

**Mineralization Defect**
- abnormal matrix
  - osteogenesis imperfecta
  - fibrogenesis imperfecta
  - axial osteomalacia
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - bisphosphonates, aluminum, high dose fluoride, anticonvulsants

**Table 36. Clinical Presentations of Rickets and Osteomalacia**

<table>
<thead>
<tr>
<th>Rickets</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal pain and deformities, bow legged</td>
<td>Not as dramatic</td>
</tr>
<tr>
<td>Fracture susceptibility</td>
<td>Diffuse skeletal pain</td>
</tr>
<tr>
<td>Weakness and hypotonia</td>
<td>Bone tenderness</td>
</tr>
<tr>
<td>Disturbed growth</td>
<td>Fractures</td>
</tr>
<tr>
<td>Rickets rosary (prominent costochondral junctions)</td>
<td>Gait disturbances (waddling)</td>
</tr>
<tr>
<td>Harrison’s groove (indentation of lower ribs)</td>
<td>Proximal muscle weakness</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Hypotonia</td>
</tr>
</tbody>
</table>

**Investigations**

**Table 37. Laboratory Findings in Osteomalacia and Rickets**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Serum Phosphate</th>
<th>Serum Calcium</th>
<th>Serum ALP</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>Decreased</td>
<td>Decreased to normal</td>
<td>Increased</td>
<td>Decreased calcitriol</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Decreased</td>
<td>Normal</td>
<td>Decreased to normal</td>
<td></td>
</tr>
<tr>
<td>Proximal RTA</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Associated with hyperchloremic metabolic acidosis</td>
</tr>
</tbody>
</table>

- Conditions associated with abnormal matrix formation: Normal

- **Radiologic findings**
  - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profunda hip deformity
  - bone biopsy: usually not necessary but considered the gold standard for diagnosis

**Treatment**
- definitive treatment depends on the underlying cause
- vitamin D supplementation
- PO₄³⁻ supplements if low serum PO₄³⁻, Ca²⁺ supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis
Renal Osteodystrophy

- changes to mineral metabolism and bone structure secondary to chronic kidney disease
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoid
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology

- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)2-Vit D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Clinical Features

- soft tissue calcifications → necrotic skin lesions if vessels involved
- osteodystrophy → generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of osteitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations

- serum Ca2+ corrected for albumin, PO43-, PTH, ALP ± imaging (x-ray, BMD), ± bone biopsy

Treatment

- prevention
  - maintenance of normal serum Ca2+ and PO43+ by restricting PO43+ intake to 1 g OD
  - Ca2+ supplements; PO43+ binding agents (calcium carbonate, aluminum hydroxide)
  - vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification

Paget’s Disease of Bone

Definition

- a metabolic disease characterized by excessive bone destruction and repair

Epidemiology

- a common disease: 5% of the population, 10% of population >80 yr old

Etiology and Pathophysiology

- postulated to be related to a slow progressing viral infection of osteoclasts, possibly paramyxovirus
- strong familial incidence
- initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis

- primary bone lesions
  - osteogenic sarcoma
  - multiple myeloma
  - fibrous dysplasia
- secondary bone lesions
  - osteitis fibrosa cystica
  - metastases

Clinical Features

- usually asymptomatic (routine x-ray finding or elevated ALP)
- severe bone pain (e.g. pelvis, femur, tibia) is often the presenting complaint
- skeletal deformities: bowed tibias, kyphosis, frequent fractures
- skull involvement: headaches, increased hat size, deafness
- increased warmth over involved bones due to increased vascularity
- high output CHF
- hypercalcemia with immobilization
- osteosarcoma

Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget’s Disease

- **Study:** Two identical, randomized, double-blind, actively controlled trials (combined for analysis).
- **Patients:** 357 men and women who were ≥30 yr and had radiologically confirmed Paget’s disease.
  - All but 4 patients had alkaline phosphatase levels that were more than twice the upper limit of normal.
- **Intervention:** One 15-min infusion of 5 mg of zoledronic acid compared with 60 d of oral risedronate (30 mg/d) with follow up at 6 mo.
- **Primary Outcome:** Rate of therapeutic response at 6 mo, defined as a normalization of alkaline phosphatase levels or a reduction of at least 75% in the total alkaline phosphatase excess.
- **Results:** At 6 mo, 96% of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3% of patients receiving risedronate (127 of 171, p<0.001). Alkaline phosphatase levels normalized in 88.6% of patients in the zoledronic acid group and 57.9% of patients in the risedronate group (p<0.001). Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 89 d, p<0.001).
- **Conclusion:** A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget’s disease than does daily treatment with risedronate.
Investigations
- laboratory
  - ↑↑ serum ALP (unless burnt out), Ca²⁺ normal or ↑, PO₄³⁻ normal
  - urinary hydroxyproline ↑ (indicates resorption)
- imaging
  - bone scan to evaluate the extent of disease
  - skeletal survey: involved bones are denser and expanded with cortical thickening
  - initial lesion may be destructive and radiolucent
  - multiple fissure fractures in long bones

Complications
- local
  - fractures, osteoarthritis
  - cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  - osteosarcoma/sarcomatous change in 1-3%
    - indicated by marked bone pain, new lytic lesions and sudden increased ALP
- systemic
  - hypercalcemia and nephrolithiasis
  - high output CHF due to increased vascularity

Treatment
- symptomatic therapy (pain management)
- weight-bearing exercise
- adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
- treat medically if ALP >3x normal
  - bisphosphonates, e.g. alendronate 40 mg PO OD x 6 mo OR risedronate 30 mg PO OD x 3 mo OR zoledronic acid 5 mg IV per yr
  - calcitonin 50-100 U/d SC
- surgery for fractures, deformity, degenerative changes

Male Reproductive Endocrinology

Androgen Regulation
- negative feedback may occur by androgens directly or after conversion to estrogen
- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

Tests of Testicular Function
- testicular size (lower limit = 4 cm x 2.5 cm)
- LH, FSH, total and/or bioavailable testosterone
- human chorionic gonadotropin (hCG) stimulation test
  - assesses ability of Leydig cell to respond to gonadotropin
- semen analysis
  - semen volume, sperm count, morphology, and motility
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility
- see Urology, U33
- deficiency in gametogenesis or testosterone production

Etiology
- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure), and idiopathic
- primary hypogonadism is more common than secondary
Table 38. Classification and Features of Hypogonadism

<table>
<thead>
<tr>
<th>Hypergonadotropic Hypogonadism (Primary Hypogonadism)</th>
<th>Hypogonadotropic Hypogonadism (Secondary Hypogonadism)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td></td>
</tr>
<tr>
<td>Primary testicular failure</td>
<td>Hypogonad-pituitary axis failure</td>
</tr>
<tr>
<td>↑ LH and FSH, ↑ FSH/LH ratio</td>
<td>↓ LH + FSH</td>
</tr>
<tr>
<td>↓ testosterone and sperm count</td>
<td>↓ testosterone and sperm count</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
</tr>
<tr>
<td>Congenital:</td>
<td></td>
</tr>
<tr>
<td>• Chromosomal defects (Klinefelter's, Noonan)</td>
<td>• Kallman's syndrome</td>
</tr>
<tr>
<td>• Cryptorchidism</td>
<td>• Prader-Willi syndrome</td>
</tr>
<tr>
<td>• Disorders of sexual development (OSD)</td>
<td>• Abnormal subunit of LH or FSH</td>
</tr>
<tr>
<td>• Bilateral anorchia (vanishing testicle syndrome)</td>
<td>• Infarction</td>
</tr>
<tr>
<td>• Myotonic dystrophy</td>
<td>• Hypo or hyperthyroidism</td>
</tr>
<tr>
<td>• Mutation of FSH or LH receptor gene</td>
<td>• Hypothalamic-pituitary disease (tumor, hyperprolactinemia, hypopituitarism)</td>
</tr>
<tr>
<td>• Disorders of androgen synthesis</td>
<td>• Drugs</td>
</tr>
<tr>
<td>Germ cell defects</td>
<td>• Alcohol, marijuana, spironolactone, ketoconazole, GnRH agonists, androgen/ estrogen/progesterin use, chronic narcotic use</td>
</tr>
<tr>
<td>Sertoli cell only syndrome</td>
<td>• Cushing's syndrome</td>
</tr>
<tr>
<td>Leydig cell aplasia/failure</td>
<td>• Hypo or hyperthyroidism</td>
</tr>
<tr>
<td>Infection/Inflammation</td>
<td>• Hypothalamic-pituitary disease (tumor, hyperprolactinemia, hypopituitarism)</td>
</tr>
<tr>
<td>• Orchitis – TB, lymphoma, mumps, legroppy</td>
<td>• Drugs</td>
</tr>
<tr>
<td>• Genital tract infection</td>
<td>• Alcohol, marijuana, spironolactone, ketoconazole, GnRH agonists, androgen/ estrogen/progesterin use, chronic narcotic use</td>
</tr>
<tr>
<td><strong>Physiological factors</strong></td>
<td>• Cushing's syndrome</td>
</tr>
<tr>
<td>• Trauma, heat, irradiation, testicular torsion, varicocele</td>
<td>• Hypothalamic-pituitary disease (tumor, hyperprolactinemia, hypopituitarism)</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>• Marijuana, alcohol, chemotherapy, ketoconazole, glucocorticoid, spironolactone</td>
<td>• Cushing's syndrome</td>
</tr>
<tr>
<td><strong>Autoimmune (antisperm antibodies)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic systemic diseases (AIDS)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
</tr>
<tr>
<td>Testicular size and consistency (soft/firm)</td>
<td>Testicular size and consistency (soft/firm)</td>
</tr>
<tr>
<td>Sperm count</td>
<td>Sperm count</td>
</tr>
<tr>
<td>LH, FSH, total, and/or bioavailable testosterone</td>
<td>LH, FSH, total, and/or bioavailable testosterone</td>
</tr>
<tr>
<td>hCG stimulation</td>
<td>Prolactin levels</td>
</tr>
<tr>
<td>Karyotype</td>
<td>MRI of hypothalamic-pituitary region</td>
</tr>
</tbody>
</table>

**Treatment**

- Testosterone replacement (improve libido, muscle mass, strength, hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
  - Side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy, uncertain effects on cardiac events/mortality in older men
  - Contraindicated if history of prostate cancer, severe LUTS associated with BPH, uncontrolled or poorly controlled CHF
- GnRH agonist to restore fertility, if hypothalamic dysfunction with intact pituitary
  - Administered SC in pulsatile fashion using an external pump
- hCG + recombinant follicular stimulating hormone (rFSH) can be used to restore fertility in cases of either hypothalamic or pituitary lesions
- Testicular sperm extraction (TESE) or microscopic sperm extraction (MICROTESE) – only if testicular tissues are not functioning

**Other Causes of Male Infertility**

- Hereditary disorders: Kartagener syndrome, cystic fibrosis
- Anatomy: hypospadias, retrograde ejaculation
- Obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- Sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- Surgery: TURP, radical prostatectomy, orchietomy

**DEFECTS IN ANDROGEN ACTION**

**Etiology**

- Complete androgen insensitivity (CAIS)
- Partial androgen insensitivity (PAIS)
- 5α-reductase deficiency
- Mixed gonadal dysgenesis
- Defects in testosterone synthesis
- Infertile male syndrome
- Undervirilized fertile male syndrome

**Etiology**

- Surgery: TURP, radical prostatectomy, orchiectomy
- Sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- Obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- Anatomy: hypospadias, retrograde ejaculation

**Other Causes of Male Infertility**

- Hereditary disorders: Kartagener syndrome, cystic fibrosis
- Anatomy: hypospadias, retrograde ejaculation
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- 5α-reductase deficiency
- Mixed gonadal dysgenesis
- Defects in testosterone synthesis
- Infertile male syndrome
- Undervirilized fertile male syndrome
Clinical Features
- depends on age of onset

Table 39. Effects of Testosterone Deficiency

<table>
<thead>
<tr>
<th>First Trimester in utero</th>
<th>Incomplete virilization of external genitalia (ambiguous genitalia)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphroditism)</td>
</tr>
<tr>
<td>Third Trimester in utero</td>
<td>Microphallic</td>
</tr>
<tr>
<td></td>
<td>Cryptorchidism (failure of normal testicular descent)</td>
</tr>
<tr>
<td>Prepuberty</td>
<td>Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair)</td>
</tr>
<tr>
<td></td>
<td>Eurachoidial body habitus (greater growth of extremity long bones relative to axial bones)</td>
</tr>
<tr>
<td></td>
<td>Poor muscle development, reduced peak bone mass</td>
</tr>
<tr>
<td>Postpuberty</td>
<td>Decrease in energy, mood, and libido</td>
</tr>
<tr>
<td></td>
<td>Fine wrinkles in corners of mouth and eyes</td>
</tr>
<tr>
<td></td>
<td>Decrease in pubic/axillary hair, hematocrit, muscle mass, strength, and BMD</td>
</tr>
</tbody>
</table>

Adapted from: UpToDate, 2010; Cecil's Essentials of Medicine

Treatment
- appropriate gender assignment in the newborn
- hormone replacement or supplementation
- psychological support
- gonadectomy for cryptorchidism (due to increased risk for testicular cancer)
- reduction mammoplasty for gynecomastia

Erectile Dysfunction
- see Urology, U30

Gynecomastia

Definition
- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals and does not warrant further evaluation

Etiology

Physiologic
- puberty
- elderly (involutional)
- neonatal (maternal hormone)

Pathologic
- endocrinopathies: primary or secondary hypogonadism, hyperthyroidism, extreme hyperprolactinemia, adrenal disease
- tumors: pituitary, adrenal, testicular, breast, ectopic production of hCG
- chronic diseases: cirrhosis, renal, malnutrition (with refeeding)
- drugs: estrogens and estrogen agonists, spironolactone, ketoconazole, cimetidine, digoxin, chemotherapy, marijuana, alcohol
- congenital/genetic: Klinefelter’s syndrome, androgen insensitivity
- other: idiopathic, familial

Pathophysiology
- hormonal imbalance due to increased estrogen activity (increased production, or increased availability of estrogen precursors for peripheral conversion to estrogen) or decreased androgen activity (decreased androgen production, binding of androgen to sex hormone binding globulin (SHBG), or androgen receptor blockage)

History
- recent change in breast characteristics
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction
Physical Exam
- signs of feminization
- breast
  - rule out red flags suggesting breast cancer: unilateral, eccentric, hard, or fixed mass, skin dimpling or retraction, and nipple discharge or crusting
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue, and no discrete mass is palpable
- genito-urinary exam
- stigmata of liver or thyroid disease

Investigations
- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated need to locate the primary tumor)
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
- testicular U/S to rule out testicular mass
- MRI of hypothalamic-pituitary region if pituitary adenoma suspected

Treatment
- initial observation for most men with gynecomastia
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen, clomiphene
- surgical
  - usually required for macromastia; gynecomastia present for >1 yr (fibrosis is unresponsive to medication); or failed medical treatment and for cosmetic purposes

Female Reproductive Endocrinology

- see Gynecology, GY4
**Paraneoplastic Syndrome**

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

**Table 40. Clinical Presentation**

<table>
<thead>
<tr>
<th>Syndrome Class</th>
<th>Symptoms/Syndrome</th>
<th>Associated Malignancies</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Cushing’s syndrome</td>
<td>Small-cell lung cancer</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuronal tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thymoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SIADH</td>
<td>Small-cell lung cancer</td>
<td>Antidiuretic hormone secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS malignancies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypercalceemia</td>
<td>Lung cancer</td>
<td>PTH-related protein, TGF-α, TNF secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ovarian carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
<td>Hepatocellular carcinoma</td>
<td>Insulin or insulin-like substance secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fibrosarcoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carcinoid</td>
<td>Pancreatic carcinoma</td>
<td>Serotonin, bradykinin secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastric carcinoma</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Lambert-Eaton myasthenic syndrome (LEMS)</td>
<td>Small-cell lung cancer</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• muscle weakness in limbs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
<td>Thymoma</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• fluctuating muscle weakness and fatigability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic limbic encephalitis</td>
<td>Small-cell lung cancer</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• depression, seizures, short-term memory loss</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Hypokalemic nephropathy</td>
<td>Small-cell lung cancer</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td>Lymphoma</td>
<td>Immune complex sedimentation in nephrons</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melanomas</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Watery diarrhea</td>
<td>Medullary thyroid carcinomas</td>
<td>Prostaglandin secretion</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Erythrocytosis</td>
<td>Renal cell carcinoma</td>
<td>EPO production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepato-cellular carcinoma</td>
<td></td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>SLE</td>
<td>Lymphomas</td>
<td>Anti-nuclear Ab production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gonadal carcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
<td>Breast carcinoma</td>
<td>Anti-nuclear Ab production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Uterine cancer</td>
<td></td>
</tr>
</tbody>
</table>

**Investigations**
- CBC, electrolytes, creatinine, LFTs, ALP, ESR, CRP, serum/urine electrophoresis,
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, PET scan
- ± endoscopy

**Treatment**
- treat underlying tumor: surgery, radiation, chemotherapy
- treat immune-mediated disorder: IVlg, steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)
## Diabetes Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>US Name</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Biguanide</strong></td>
<td>Stimulates insulin release from β cells by causing K⁺ channel closure to depolarization → Ca²⁺ mediated insulin release</td>
<td>metformin</td>
<td>Glucophage® Glimeza®</td>
<td>500 mg OD titrated to 2000 mg/d maximum</td>
<td>Useful in obese type 2 DM</td>
<td>Moderate to severe liver dysfunction</td>
<td>GI upset (abdominal discomfort, bloating, diarrhea)</td>
<td>↓ HbA1c 1.0-2.0%</td>
</tr>
<tr>
<td></td>
<td>Increases glucose uptake</td>
<td></td>
<td></td>
<td></td>
<td>Improves both fasting and postprandial hyperglycemia</td>
<td>Moderate renal dysfunction GFR &lt;30 mL/min</td>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreases hepatic glucose production by stimulation of hepatic AMP-activated protein kinase (AMPK)</td>
<td></td>
<td></td>
<td></td>
<td>Also ↓ TG</td>
<td>Cardiac dysfunction</td>
<td>Antinina</td>
<td></td>
</tr>
<tr>
<td><strong>Insulin Secretagogue</strong></td>
<td>Stimulates insulin release</td>
<td>sulfonylureas:</td>
<td>Micronase® Glyburide®</td>
<td>2.5-5.0 mg/d titrated to &gt;5 mg bid</td>
<td>Moderate to severe liver dysfunction</td>
<td>Moderate to severe liver dysfunction</td>
<td>Hypoglycemia</td>
<td>↓ HbA1c 1.0-2.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>glipizide</td>
<td>Glynase PreTab®</td>
<td>40-160 mg bid</td>
<td></td>
<td>Other medications and circumstances:</td>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>gliclazide</td>
<td>Diamoxir® Diamoxir® MR</td>
<td>30-120 mg OD</td>
<td></td>
<td>Cardiac dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>glimepiride</td>
<td>Amaryl®</td>
<td>1-8 mg OD</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>non-sulfonylureas:</td>
<td>Gliclazide</td>
<td>2.5-5.0 mg/d titrated to &gt;5 mg bid</td>
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<tr>
<td></td>
<td></td>
<td>repaglinide</td>
<td>Micronase®</td>
<td>0.5-4 mg tid</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>nateglinide</td>
<td>Starlix®</td>
<td>60-120 mg tid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Insulin Sensitizers (thiazolidinedione)</strong></td>
<td>Sensitizes peripheral tissues to insulin</td>
<td>rosiglitazone</td>
<td>Avandia®</td>
<td>2-8 mg OD</td>
<td></td>
<td>Severe liver dysfunction</td>
<td>Peripheral edema</td>
<td>↓ HbA1c 1.0-1.5%</td>
</tr>
<tr>
<td></td>
<td>Increases glucose uptake</td>
<td>pioglitazone</td>
<td>Actos®</td>
<td>15-45 mg OD</td>
<td></td>
<td>Other medications and circumstances:</td>
<td>CHF</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreases FFA release from adipose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiac dysfunction</td>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Binds to nuclear receptor PPAR-γ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fluid retention and CHF</td>
<td>Increased risk of cardiac events with rosiglitazone (requires written informed consent when prescribing)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fractures</td>
<td>Increased risk of bladder cancer with pioglitazone</td>
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</tr>
<tr>
<td><strong>α-Glucosidase Inhibitor</strong></td>
<td>Inhibits carbohydrate GI absorption by inhibiting brush border α-glucosidase</td>
<td>acarbose</td>
<td>Glucobay®</td>
<td>25 mg OD titrated to 100 mg tid</td>
<td></td>
<td></td>
<td>Flatulence</td>
<td>↓ HbA1c 0.5-1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postprandial hyperglycemia</td>
<td>Abdominal cramps</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td><strong>Dipeptidyl Peptidase IV (DPP-IV) Inhibitor</strong></td>
<td>Inhibits degradation of endogenous antihyperglycemic incretin hormones</td>
<td>sitagliptan</td>
<td>Januvia®</td>
<td>100 mg OD</td>
<td></td>
<td>Other medications and circumstances:</td>
<td>Nasopharyngitis</td>
<td>↓ HbA1c 0.5-1.0%</td>
</tr>
<tr>
<td></td>
<td>Incretin hormones stimulate insulin secretion, inhibit glucagon release, and delay gastric emptying</td>
<td>saxagliptin</td>
<td>Onglyza®</td>
<td>2.5-5 mg OD</td>
<td></td>
<td></td>
<td>URI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>linagliptin</td>
<td>Trajenta®</td>
<td>5 mg OD</td>
<td></td>
<td></td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pancreatitis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stevens-Johnson syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>Glucagon-Like Peptide-1 (GLP-1) Analogue</strong></td>
<td>Binds to GLP-1 receptor to promote insulin release</td>
<td>Exenatide</td>
<td>Byetta®</td>
<td>5-10 µg SC bid 1 h before meals</td>
<td></td>
<td>Other medications and circumstances:</td>
<td>Nausea, diarrhea</td>
<td>↓ HbA1c 1.0-1.5%</td>
</tr>
<tr>
<td></td>
<td>Insulinotropic effect suppressed as plasma glucose &lt;4 mmol/L</td>
<td>Liraglutide</td>
<td>Victozza®</td>
<td>0.6-1.8 mg OD SC</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Slows gastric emptying, suppresses inappropriately elevated glucagon levels</td>
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<td></td>
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<tr>
<td></td>
<td>Causes β-cell regeneration and differentiation in vitro</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

For insulin formulations see Table 9, E9
### Dyslipidemia Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>US Name</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA Reductase Inhibitor</td>
<td>• Inhibits cholesterol biosynthesis, ↑ LDL synthesis, ↓ HDL, limited ↓ VLDL</td>
<td>atorvastatin</td>
<td>Lipitor®</td>
<td>10-80 mg/d</td>
<td>• 1st line monotherapy</td>
<td>• Active liver disease</td>
<td>• GI symptoms, ↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑→</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluvastatin</td>
<td>Lescol®</td>
<td>20-80 mg/d</td>
<td>Used for ↑ LDL, ↑ TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pravastatin</td>
<td>Pravachol®</td>
<td>10-40 mg/d</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>rosuvastatin</td>
<td>Crestor®</td>
<td>10-80 mg/d</td>
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<tr>
<td></td>
<td></td>
<td>simvastatin</td>
<td>Zocor®</td>
<td>10-80 mg/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrates</td>
<td>• Upregulate lipoprotein lipase + apo A1, ↓ VLDL, ↓ TG, modest ↓ LDL, modest ↑ HDL</td>
<td>bezafibrate</td>
<td>Bezalip®</td>
<td>400 mg/d</td>
<td>• Used for ↑ TG, hypercholesterolemia</td>
<td>• Hepatic disease, Renal disease</td>
<td>• GI upset, Skin rashes, ↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑↑→</td>
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<tr>
<td></td>
<td></td>
<td>fenofibrate</td>
<td>Lipidil®</td>
<td>48-200 mg/d</td>
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<tr>
<td></td>
<td></td>
<td>gemfibrozil</td>
<td>Lopid®</td>
<td>600-1200 mg/d</td>
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</tr>
<tr>
<td>Niacin</td>
<td>• Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL; decreased clearance of HDL</td>
<td>nicotinic acid</td>
<td>Niacor®</td>
<td>0.5-2 g/d</td>
<td>• Used for ↑ LDL, ↑ VLDL</td>
<td>• Hypersensitivity, Hepatic dysfunction, Active PUD, Hyperuricemia</td>
<td>• Generalized flushing, Abnormal liver enzymes, Pruritis, IGT, Watch glucose control with overt DM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>generic niacin</td>
<td>generic niacin</td>
<td>1-3 g/d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>• Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓ LDL</td>
<td>cholestyramine</td>
<td>Questran®</td>
<td>2-24 g/d</td>
<td>• Used for ↑ LDL, ↑ TG</td>
<td>• Complete biliary obstruction, Pregnancy, lactation, TG &gt; 3.5 mmol/L, GI motility disorder</td>
<td>• Constipation, Nausea, Flatulence, Bloating, Rise in TG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>colestipol</td>
<td>Colestid®</td>
<td>5-30 g/d</td>
<td>• Used as adjunct with statins or fibrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol Absorption</td>
<td>• Inhibits cholesterol absorption at the small intestine brush border</td>
<td>ezetimibe</td>
<td>Zetia®</td>
<td>10 mg/d</td>
<td>• Used for ↑ LDL, apo-B</td>
<td>• Hypersensitivity, Hepatic dysfunction, Do not combine with fibrates or bile acid resins</td>
<td>• Fatigue, Pharyngitis, Sinusitis, Abdominal pain, Danazol, Antithyroidal</td>
</tr>
<tr>
<td>Inhibitors</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

### Thyroid Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>US Name</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid Agent (thionamides)</td>
<td>• Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T4 and T3; PTU also interferes with conversion of T4 to T3</td>
<td>propylthiouracil (PTU)</td>
<td>Propyl-Thyrate®</td>
<td>Start 100 mg PO tid, then adjust accordingly</td>
<td>• Hyperthyroidism</td>
<td>• Hypersensitivity, Relative: renal failure, liver disease, PTU recommended in 1st trimester, MMI during 2nd and 3rd trimester, Lactation: safe with PTU &lt;300 mg/day and MMI &lt;20-30 mg/d</td>
<td>• N/V, Rash, Drug-induced hepatitis, Agranulocytosis, Hepatotoxicity, Cholestasis with MMI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>methimazole (MMI)</td>
<td>Tapazole®</td>
<td>Start 5-20 mg PO OD, then adjust accordingly Up to 60 mg OD may be required</td>
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</tr>
<tr>
<td>Thyroid Hormone</td>
<td>• Synthetic form of thyroxine (T4)</td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.2 mg/d, usually 1.8x weight (kg) is dose in micrograms In elderly patients start at 0.025 mg/d</td>
<td>• Hypothyroidism</td>
<td>• Recent MI, Thyroiditis</td>
<td>• If wrong dosing: symptoms of hypothyroidism or hyperthyroidism, Skin rash from dye in pill</td>
</tr>
<tr>
<td></td>
<td></td>
<td>l-thyroxine</td>
<td>Levoxyl®</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Antithyroid Agent Radiopharmaceutical</td>
<td>• Radioactive isotope of iodine that is incorporated into the thyroid gland irradiating the area and destroying local glandular tissue</td>
<td>sodium iodide I-131</td>
<td>Iodotope®</td>
<td></td>
<td>• Hyperthyroidism</td>
<td>• Hypersensitivity, Concurrent antithyroid medication, Pregnancy, lactation</td>
<td>• N/V, Bone marrow suppression, Skin rashes, Hypothyroidal</td>
</tr>
</tbody>
</table>
# Metabolic Bone Disease Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Bisphosphonates                  | • Inhibits osteoclast-mediated bone resorption                                      | alendronate       | Fosamax®    | Osteoporosis: 5-10 mg OD 70 mg once weekly Paget’s: 40 mg OD for 6 mo | • Prevention of postmenopausal osteoporosis  
• Treatment of osteoporosis  
• Glucocorticoid-induced osteoporosis  
• Paget’s disease | • Esophageal stricture or achalasia (oral)  
• Unable to stand or sit upright for >30 min (oral)  
• Hypersensitivity  
• Hypocalcemia  
• Renal insufficiency | • GI  
• MSK pain  
• Headache  
• Osteonecrosis of the jaw  
• Atypical femoral shaft fractures |
|                                  |                                                                                     | risedronate       | Actonel®    | Osteoporosis: 5 mg OD 35 mg once weekly 150 mg once monthly Paget’s: 30 mg OD for 2 mo | • Treatment and prevention of postmenopausal osteoporosis  
• Treatment and prevention of glucocorticoid-induced osteoporosis  
• Paget’s disease | • Symptomatic Paget’s disease  
• Prevention and treatment of heterotopic ossification after total hip replacement or spinal cord injury | |
|                                  |                                                                                     | etidronate        | Didronel®   | Paget’s: 5-10 mg qd OD x 6 mo             | • Treatment and prevention of postmenopausal osteoporosis  
• Paget’s disease | • Prevention and treatment of glucocorticoid-induced osteoporosis  
• Paget’s disease | |
|                                  |                                                                                     | ibandronate       | Boniva®     | 2.5 mg OD or 150 mg once monthly          | • Treatment and prevention of postmenopausal osteoporosis (US only)  
• Prevention and treatment of glucocorticoid-induced osteoporosis  
• Paget’s disease | • Prevention and treatment of glucocorticoid-induced osteoporosis  
• Paget’s disease | |
|                                  |                                                                                     | pamidronate       | Aredia®     | Hypercalcemia of malignancy 60-90 mg IV over 2-24 h Wait at least 7 d before considering retreatment | • Hypercalcemia of malignancy  
• Paget’s disease  
• Osteolytic bone metastases of breast cancer  
• Osteolytic lesions of multiple myeloma | |
|                                  |                                                                                     | zoledronate       | Zometa®  
Aclasta® | 5 mg IV once yearly IV | • Treatment of osteoporosis  
• Hypercalcemia of malignancy  
• Treatment and prevention of skeletal complications related to cancer | | |
| Selective Estrogen Receptor Modulators | • Decreases resorption of bone through binding to estrogen receptors | raloxifene        | Evista®     | 60 mg OD | • Treatment and prevention of postmenopausal osteoporosis (2nd line) | • Lactation  
• Pregnancy  
• Active or past history of DVT, PE, or retinal vein thrombosis | • Hot flushes  
• Leg cramps  
• Increased risk of fatal stroke, versus thromboembolism | |
| Calcitonin                       | • Inhibits osteoclast-mediated bone resorption                                      | calcitonin        | Miacalcin®  | One spray (200 IU) per day, alternating nostrils | • Treatment of postmenopausal-osteoporosis, greater than 5 yr postmenopause | • Clinical allergy to salmon-calcitonin | • Rhinitis  
• Epistaxis  
• Sinusitis  
• Nasal dryness | |
| Anti-RANKL Monoclonal Ab         | • Inhibits RANKL (osteoclast differentiating factor) → inhibit osteoclast formation and decrease bone resorption | denosumab         | Xgeva™      | 60 mg SC q6mo | • Treatment of postmenopausal women at high risk of fracture  
• Prevent skeletal-related events in patients with bone metastasis from solid tumors | • Hypocalcemia  
• Fatigue/headache  
• Dermatitis/rash  
• Hypophosphatemia/Hypocalcemia  
• Hypercholesterolemia  
• GI discomfort | |
| PTH                              | • Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity | teriparatide      | Forteo®     | 20 µg SC OD x 18-24 mo | • Treatment of postmenopausal women with osteoporosis who are at high risk for fracture  
• Treatment of men with primary or hypogonadal osteoporosis who are at high risk for fracture | • Paget’s disease  
• Prior external beam or implant radiation therapy involving the skeleton  
• Bone metastases  
• Metabolic bone diseases other than osteoporosis | • Orthostatic hypotension  
• Hypocalcemia  
• Dizziness  
• Leg cramps |
### Metabolic Bone Disease Medications (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>US Name</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>• Inhibits PTH secretion</td>
<td>cholecalciferol (vitamin D3)</td>
<td>Vitamin D</td>
<td>800-2000 IU/d</td>
<td>• Osteopenia</td>
<td>• Caution with renal stones</td>
<td>• Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ergocalciferol (vitamin D2)</td>
<td></td>
<td>50,000 IU/wk</td>
<td>• Osteopenia</td>
<td></td>
<td>• Constipation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>calcitriol (1,25(OH)2-D)</td>
<td></td>
<td>Start 0.25 µg/d Titrate up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d</td>
<td>• Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis</td>
<td></td>
<td>• Constipation</td>
</tr>
</tbody>
</table>

### Adrenal Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mineralocorticoid Activity</th>
<th>Generic Drug Name</th>
<th>Potency (Relative to Cortisol)</th>
<th>Equivalent Dose (mg)</th>
<th>Duration of Action (t1/2 in h)</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>Cortef</td>
<td>1.0</td>
<td>20</td>
<td>8</td>
<td>Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q8h (continuous infusion x 24-48 h) PO once stable (50 mg q8h x 48 h, then taper over 14 d) Chronic AI: 15-20 mg PO OD (2/3 AM, 1/3 PM)</td>
<td>• In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low K+ metabolic alkalosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Solu-Cortef</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone Acetate</td>
<td>Yes</td>
<td>Cortisone Acetate</td>
<td>0.8</td>
<td>25</td>
<td>oral = 8 IM = 18+</td>
<td>Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24h Chronic AI: 25 mg/d</td>
<td>• Pre-drug which is converted to active form as hydrocortisone • High doses can result in mineralocorticoid side effects (see above)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>No</td>
<td>Prednisone</td>
<td>4</td>
<td>5</td>
<td>16-36</td>
<td>Adrenal Crisis: 15-60 mg/d PO qtid or divided bid/qid Chronic AI: 5 mg daily</td>
<td>• Pre-drug which is converted to active form as prednisolone</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>No</td>
<td>Dexamethasone</td>
<td>30</td>
<td>0.7</td>
<td>36-54 Adrenal Crisis: 4 mg IV, repeat q2-6h if necessary</td>
<td>Used for undiagnosed adrenal insufficiency (does not interfere with measurement of serum cortisol levels)</td>
<td></td>
</tr>
</tbody>
</table>
# Landmark Endocrinology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIABETES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>NEJM 2008; 358:2560-72</td>
<td>Compared with standard therapy the use of intensive therapy to target normal HbA1c levels (&lt;6%) for 3.5 yr increased mortality and did not significantly reduce major cardiovascular events</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>NEJM 2008; 358:2545-59</td>
<td>Intensive glucose control that lowered the HbA1c value to 6.5% reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events, or death from any cause; hypoglycemia was more common in the intensive control group</td>
</tr>
<tr>
<td>BARI-2D</td>
<td>NEJM 2009; 360:2503-15</td>
<td>In patients with both type 2 DM and CAD no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin</td>
</tr>
<tr>
<td>DCCT</td>
<td>NEJM 1993; 329:977-86</td>
<td>Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy, and neuropathy) in type 1 DM</td>
</tr>
<tr>
<td>EDIC</td>
<td>NEJM 2005; 353:2644-53</td>
<td>Compared with conventional therapy intensive DM therapy early on without macrovascular disease (goal HbA1c &lt;6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with type 1 DM</td>
</tr>
<tr>
<td>Look AHEAD</td>
<td>NEJM 2013; 369:145-54</td>
<td>Moderate weight loss (&lt;7% BW) and increased exercise are not associated with reduction in CVD and its complications among overweight or obese patients with type 2 DM</td>
</tr>
<tr>
<td>NAVIGATOR</td>
<td>NEJM 2010; 362:1463-90</td>
<td>In patients with impaired glucose tolerance, nateglinide did not reduce progression to DM or risk of cardiovascular events while valsartan only reduced progression to DM</td>
</tr>
<tr>
<td>PREDIMED</td>
<td>NEJM 2013; 368:1279-90</td>
<td>A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, CVA, or CV death in those at high risk for CV disease (outcome was driven by reduction in rates of CVA)</td>
</tr>
<tr>
<td>Steno-2</td>
<td>NEJM 2008; 358:580-91</td>
<td>In at-risk patients with type 2 DM intensive intervention with multiple drug combinations and behavior modification had sustained significant beneficial effects with respect to vascular complications and mortality; multifactorial intervention is critical in the management of type 2 DM</td>
</tr>
<tr>
<td>UKPDS Extension</td>
<td>NEJM 2008; 359:1577-89</td>
<td>Continued risk reduction in microvascular risk and emergent risk reductions for MI and death from any cause 10 yr post UKPDS trial follow up in type 2 DM</td>
</tr>
<tr>
<td>VADT</td>
<td>NEJM 2009; 360:1-11</td>
<td>In patients with longstanding poorly controlled type 2 DM intensive glucose control had no significant effect on the rates of major cardiovascular events, death, or microvascular complications; adverse events, predominantly hypoglycemia, were more common in the intensive control group</td>
</tr>
<tr>
<td><strong>LIPIDS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>Lancet 1994; 344:1383-89</td>
<td>In patients with angina or previous MI and high total cholesterol simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty</td>
</tr>
<tr>
<td>FIELD</td>
<td>Lancet 2005; 366:1849-61</td>
<td>In patients with type 2 DM not previously on statin therapy fenofibrate did not significantly reduce the risk of the primary outcome of coronary events; it did reduce non-fatal MIs and revascularizations</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002; 380:7-22</td>
<td>In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths, and major vascular events</td>
</tr>
<tr>
<td>Jupiter</td>
<td>NEJM 2008; 359:2195-207</td>
<td>Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity CRP levels and no hyperlipidemia</td>
</tr>
<tr>
<td>TNT</td>
<td>NEJM 2005; 352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d</td>
</tr>
</tbody>
</table>
References

Roff DS. Disorders that cause hypothyroidism. Rose BD (editor). Waltham: UpToDate. 2002.
Periodic Health Examination

- American Academy of Family Physicians (AAFP) represents 115,900 primary care physicians and student members nationwide
- approximately one in four of all office visits are made to family physicians (214 million office visits each yr)
- basis for recommendations is the analysis of scientific knowledge available as presented by the US Preventive Services Task Force (USPSTF) in the Guide to Clinical Preventive Services and ongoing updates
- recommendations are based on systematic analysis of scientific evidence
- most notable recommendation is the abolition of the annual physical exam; replaced by the PHE

Purpose of the PHE

- **primary prevention**: identify risk factors for common diseases; counsel patients to promote healthy behavior
- **secondary prevention**: presymptomatic detection of disease to allow early treatment and to prevent disease progression
- update clinical data
- enhance patient-physician relationship

AAFP Grading System (for recommendations before 2007)

- the recommendations include the examinations that should be offered (strongly recommend and recommend), those that should not be done (recommend against), those considered an option (no recommendation for or against), and those with insufficient evidence to recommend for or against
- **strongly recommend**: good quality evidence exists that demonstrates substantial net benefit over harm; the intervention is perceived to be cost effective and acceptable to nearly all patients
- **recommend**: although evidence exists that demonstrates net benefit, the benefit is only moderate in magnitude or the evidence supporting a substantial benefit is only fair; the intervention is perceived to be cost effective and acceptable to most patients
- **no recommendation for or against**: good or fair evidence exists of at least a small net benefit; cost effectiveness may not be known or patients may be divided about acceptability of the intervention
- **recommend against**: good or fair evidence that demonstrates no net benefit over harm
- **insufficient evidence to recommend for or against**: no evidence of even fair quality exists, or the existing evidence is conflicting

AAFP Grading System (for recommendations after 2007)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Suggestions for Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is substantial</td>
<td>Offer or provide this service</td>
</tr>
<tr>
<td>B</td>
<td>The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial</td>
<td>Offer or provide this service</td>
</tr>
<tr>
<td>C</td>
<td>The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small</td>
<td>Offer or provide this service for selected patients depending on individual circumstances</td>
</tr>
<tr>
<td>D</td>
<td>The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits</td>
<td>Discourage the use of this service</td>
</tr>
<tr>
<td>I Statement</td>
<td>The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined</td>
<td>Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms</td>
</tr>
</tbody>
</table>

Patient-Centered Clinical Method
- Explore/define patient problems and decide on management together
- Consider both agendas and find common ground

Agendas in Family Medicine
- **Doctor’s Agenda**
  - History, physical, investigations, diagnosis, plan
- **Patient’s Agenda**
  - FIFE
    - Feelings: related to the illness, fears (how do you feel about what is happening?)
    - Ideas: and explanations of the cause (what do you think is going on?)
    - Function: the illness’ impact on daily life (how is it affecting your work or life?)
    - Expectations: of the doctor and the illness (what were you expecting at the visit?)

Adult Periodic Health Exam
- Male and female evidence-based preventive care checklist forms are available online at http://www.aafp.com

When Ordering Fasting Blood Work
- Routinely ordered as ≥12 h of fasting
- Remember, “fasting” means no food, no drinks (except small quantities of water), no gum, no smoking
- Prescription medications are okay unless otherwise specified
- Special care should be taken when ordering fasting blood work in elderly or other medically fragile patients

Note About PSA
- Routine PSA screening is currently not recommended
- PSA testing is used in ongoing surveillance and management of men with prostate cancer (see Urology, U25)
Table 1. AAFP Recommendations for the Periodic Health Exam

<table>
<thead>
<tr>
<th>Health Concern</th>
<th>AAFP Recommends</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal Aortic Aneurysm</td>
<td>One-time screening by U/S in men ages 65 to 75 who have ever smoked (2014)</td>
<td>B</td>
</tr>
<tr>
<td>Intimate Partner Violence</td>
<td>Screening all women of childbearing age for intimate partner violence (2013)</td>
<td>B</td>
</tr>
<tr>
<td>Alcohol Misuse, Adults</td>
<td>Screening adults aged 18 yr or older for alcohol misuse and provide persons in risky or hazardous drinking with brief behavioral counseling interventions</td>
<td>B</td>
</tr>
<tr>
<td>Bacteria, Asymptomatic</td>
<td>Screening for asymptomatic bacteria with urine culture for pregnant women at 12 to 16 wk gestation or at the first prenatal visit, if later (2008)</td>
<td>A</td>
</tr>
<tr>
<td>Behavioral Counseling to Prevent STD</td>
<td>High-intensity behavioral counseling all sexually active adolescents and for adults at increased risk for STDs (2008)</td>
<td>B</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>Interventions during pregnancy and after birth to promote and support breastfeeding (2008)</td>
<td>B</td>
</tr>
<tr>
<td>Cardiovascular Disease, Aspirin for the Prevention of</td>
<td>The use of aspirin for women age 45 to 79 when benefit of reduction in MI outweighs potential harm of GI bleed (2009)</td>
<td>A</td>
</tr>
<tr>
<td>Cardiovascular Disease, Aspirin for the Prevention of</td>
<td>The use of aspirin for women age 55 to 79 when benefit of reduction in strokes outweighs potential harm of increase in GI bleed (2009)</td>
<td>A</td>
</tr>
<tr>
<td>Chlamydia, Women</td>
<td>Screening for chlamydial infection for all sexually active non-pregnant young women aged 24 and younger and for older non-pregnant women who are at increased risk (2007)</td>
<td>A</td>
</tr>
<tr>
<td>Congenital Hypothyroidism</td>
<td>Screening for congenital hypothyroidism in newborns (2008)</td>
<td>A</td>
</tr>
<tr>
<td>Dental Caries, in Children (Birth through Age 5)</td>
<td>Primary care clinicians apply fluoride varnish to primary teeth of all infants and children starting at the age of primary tooth eruption and prescribe oral fluoride supplementation starting at age 6 mo for children whose water supply is deficient in fluoride (2014)</td>
<td>A</td>
</tr>
<tr>
<td>Depression, Adults</td>
<td>Screening adults for depression when staff-assisted depression care supports are in place to assure accurate diagnosis, effective treatment, and follow-up <strong>“Staff-assisted depression care supports” refers to clinical staff that assist the primary care clinician by providing some direct depression care and/ or coordination, case management, or mental health treatment (2010)</strong></td>
<td>A</td>
</tr>
<tr>
<td>Depression, Children and Adolescents</td>
<td>Screening of adolescents (12-18 yr of age) for major depressive disorder (MDD) when systems are in place to ensure accurate diagnosis, psychotherapy (cognitive behavioral or interpersonal), and follow-up (2009)</td>
<td>B</td>
</tr>
<tr>
<td>DM, Gestational</td>
<td>Screening for gestational DM in asymptomatic pregnant women after 24 wk of gestation (2014)</td>
<td>B</td>
</tr>
<tr>
<td>DM, Type 2</td>
<td>Screening for type 2 DM in asymptomatic adults with sustained blood pressure (either treated or untreated) &gt;135/80 mmHg (2008)</td>
<td>B</td>
</tr>
<tr>
<td>Falls Prevention in Older Adults</td>
<td>Exercise or physical therapy and vitamin D supplementation in community-dwelling adults aged 65 yr or older who are at increased risk for falls; see Clinical Considerations for information on risk assessment (2012)</td>
<td>A</td>
</tr>
<tr>
<td>Gonococcal Infection in Neoneates</td>
<td>Strongly recommends prophylactic ocular topical medication for all newborns against gonococcal ophthalmia neonatorum (2005)</td>
<td>A</td>
</tr>
</tbody>
</table>

**Health Concern**

**AAFP Recommends**

**Grade**

**Healthy Diet**

Intensive behavioral dietary counseling for adult patients with hyperlipidemia and other known risk factors for cardiovascular and dia betic-related chronic disease. Intensive counseling can be delivered by primary care physicians or by other qualified professionals including dietitians and nutritionists (1996)

**Hearing Loss (Sensorineural)**

Screening for hearing loss in all newborn infants (2008)

**Hemoglobinopathies, Newborns**

Strongly recommends ordering screening tests for PKU, hemoglobinopathies, and thyroid function abnormalities in neonates (2007)

**Hepatitis B & C**

Screening for HBV and HCV infection in persons at high risks for infection. Also offering one-time screening for HCV infection to adults born between 1945 and 1965 (2013)

**HIV Infection, Adolescents and Adults**

That clinicians screen adolescents and adults ages 18 to 65 yr for HIV infection. Younger adolescents and older adults who are at increased risk should also be screened; refer to USPSTF guidelines for more detail

**HTN, Adults**

Screening for high blood pressure in adults aged 18 and older (2007)

**Immunization**

Immunizing all children 0-19 yr of age and all adults using AAFP guidelines unless contraindicated (2014)

**Folic Acid Supplementation, Women**

That all women planning or capable of pregnancy take a daily supplement containing 0.4-1.0 mg of folic acid (2009)

**Sexually Transmitted Diseases (STDs)**

High-intensity behavioral counseling of pregnant sexually transmitted diseases (STDs) for all sexually active adolescents and for adults at increased risk for STDs (2008)

**Skin Cancer, Behavioral Counseling**

Counseling children, adolescents, and young adults ages 10 to 24 yr who have fair skin about minimizing their exposure to ultraviolet radiation to reduce risk of skin cancer (2012)

**Tobacco Use, Adults**

Screening all adults for tobacco use and provide tobacco cessation interventions for those who use tobacco products (2009)

**Vision Screening, Children**

Vision screening for all children at least once between the ages of 3 and 5 yr to detect the presence of amblyopia or its risk factors (2011)

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**Efficacy of Human Papillomavirus Vaccines – A Systematic Review**

*J. Gen. Intern. Med. 2009;24(10 Suppl)*

**Main Outcome:** Prevention of cytologically and/or histologically proven lesions (including LSIL, HSIL, VIN, VAIN, AIS, adenocarcinoma, site of the cervix, or the cervix associated with HPV infection).

**Results:** Bruised and quadrivalent vaccines reduced the rate of lesions in the cervix, vulva, vagina, and anogenital region with efficacy of 93% and 62%, respectively.

---

**Folic Acid Supplementation in Pregnancy (Joint SOGC-Motherisk Clinical Guideline)**

- To prevent neural tube defects in all women capable of becoming pregnant
- Low risk women (no personal health risks, planned pregnancy): 0.4-1.0 mg daily folic acid supplementation for at least 2-3 mo before conception and throughout pregnancy and postpartum period
- High risk women (health risks including epilepsy, insulin dependent DM, BMI >35, family history of NTDL, high risk ethnic group): at least 3 mo prior to conception until 10-12 wk post conception; daily folic acid supplementation with multivitamins with 5 mg folic acid
- From wk 12 post-conception until postpartum period: 0.4-1.0 mg of folic acid supplementation is sufficient
- Women with additional lifestyle issues (poor compliance with medications, no birth control, additional teratogenic substances): higher folic acid dose of 5 mg

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**Prostate Cancer Mortality at 11 Year of Follow-Up**

*NEJM 2012;366:981-990*

**Study:** Updated ERSPC study – multicenter randomized trial of screening for prostate cancer using PSA.

**Patients:** 162,308 men, ages 55-69 from 8 different European countries.

**Intervention:** PSA-based screening

**Main Outcome:** mortality from prostate cancer

**Results:** After median follow-up of 11 yr, the RRR of death from prostate cancer was 21%. The ARR was 1.07 deaths/1000 men. NTDL = therefore to prevent one death from prostate cancer at 11 yr follow up, 1,055 men would need to be screened.

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**Appropriate Use of Screening and Diagnostic Tests to Foster High-Value, Cost-Conscious Care**

*Ann Intern Med 2012;156:147-149*

**Suggested principles for providing high-value, cost-conscious care (see article Table 1 for specific examples):**

1. Diagnostic tests should not be performed if the results will not change management.
2. When the pretest probability of disease is low, the likelihood of a false-positive test result is higher than the likelihood of a true-positive result. False-positive results often lead to further testing, which may be expensive and potentially harmful (e.g., anxiety for patient, inappropriate treatment).
3. The true cost of a test includes not only the cost of the test itself but also the downstream costs incurred because the test was performed. These include the costs of subsequent testing, treatment, or follow-up.

**See Choosing Wisely - a campaign to help physicians and patients make smart and effective choices to ensure high-quality care.** http://www.choosingwisely.org.
Table 1. AAFP Recommendations for the Periodic Health Exam (continued)

<table>
<thead>
<tr>
<th>Health Concern</th>
<th>AAFP Recommends AGAINST</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>Screening asymptomatic adults for COPD using spirometry (2008)</td>
<td>D</td>
</tr>
<tr>
<td>Hormone Replacement Therapy</td>
<td>The use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women (2012)</td>
<td>D</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>Prostate-specific antigen (PSA)-based screening for prostate cancer (2012)</td>
<td>D</td>
</tr>
<tr>
<td>Testicular Cancer</td>
<td>Screening for testicular cancer in asymptomatic adolescent or adult males (2011)</td>
<td>D</td>
</tr>
<tr>
<td>Thyroid Cancer</td>
<td>The use of ultrasound screening for thyroid cancer in asymptomatic persons (1996)</td>
<td>D</td>
</tr>
</tbody>
</table>

- more detailed recommendations: Breast Cancer FM4, Colorectal Cancer FM4, Osteoporosis FM47, Obesity FM7

Breast Cancer Screening Guidelines

2013 Recommendations on Screening for Breast Cancer in Average-Risk Women (USPSTF)

- average-risk women: women age 40-74 with no personal history of breast cancer, history of breast cancer in 1st degree relatives, known mutations of the BRCA1/BRCA2 genes or previous exposures of the chest wall to radiation

Mammography

- age <50: recommend that decision to conduct screening mammography should be individualized and take into account patient context including her risks as well as values regarding specific benefits and harms (Grade C)
- age 50-74: recommend routine screening q2yr (Grade B)
- age 75+: current evidence is insufficient to assess benefits and harms of screening mammography (Grade I)

Magnetic Resonance Imaging

- current evidence insufficient to assess benefits and harms of MRI or digital mammography as screening modalities for breast cancer (Grade I)

Clinical Breast Examination

- current evidence insufficient to assess benefits and harms of CBE for women age 40 and older (Grade I)

Breast Self-Examination

- AAFP recommends against clinicians teaching women CBE (Grade D)

Prevention Medication

- AAFP recommends that clinicians engage in shared, informed decision making with women who are at increased risk for breast cancer about medications to reduce their risk
- for women who are at increased risk for breast cancer and at low risk for adverse medication effects, clinicians should offer to prescribe risk-reducing medications such as tamoxifen or raloxifene (Grade B)

BRCA Mutation Testing

- the AAFP recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with one of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2)
- women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing (Grade B)
- for more information on breast cancer and benign breast lesions, see General Surgery, GS54

Colorectal Cancer Screening Guidelines

- recommendations for average risk individuals (asymptomatic, no family history of UC, polyps, or CRC)
  - note: individuals with a personal history of cancer or adenomatous polyps should be followed by a surveillance regimen (screening guidelines are not applicable)
  - the AAFP recommends screening for CRC using fecal occult blood testing (FOBT), sigmoidoscopy, or colonoscopy, in adults 50-75 yr with the following intervals (Grade A recommendation)
    - annual screening with high-sensitivity FOBT
    - sigmoidoscopy every 5 yr, with high-sensitivity FOBT q3yr
    - screening colonoscopy q10yr
  - the AAFP recommends against routine screening for CRC in adults 76-85 yr (Grade C) and 85+ (Grade D)
• the USPSTF recommends against the use of aspirin or NSAIDs for the primary prevention of CRC (Grade C)
• the AAFP concludes that the evidence is insufficient to assess the benefits and harms of CT colonography and fecal DNA testing as screening modalities for CRC (Grade I recommendation)
• the AAFP recommends offering genetic testing for Lynch syndrome to patients diagnosed with CRC to reduce morbidity and mortality in relatives
  - genetic testing should be offered to 1st degree relatives of patients with Lynch syndrome, and those positive for Lynch syndrome should be offered earlier and more frequent CRC screening
• for more information on colorectal neoplasms, see General Surgery, GS33

Health Promotion and Counseling

• health promotion is the most effective preventive strategy
• 40–70% of productive life lost annually is preventable
• there are several effective ways to promote healthy behavioral change, such as discussions appropriate to a patient's present stage of change
• for more information about motivational interviewing, see http://www.motivationalinterviewing.org
Motivational Strategies for Behavioral Change

<table>
<thead>
<tr>
<th>Patient’s Stage of Change</th>
<th>Physician’s Aim</th>
<th>Physician’s Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Contemplation</td>
<td>Encourage patient to consider the possibility of change</td>
<td>Raise issue in a sensitive manner</td>
</tr>
<tr>
<td></td>
<td>Assess readiness for change</td>
<td>Offer (not impose) a neutral exchange of information to avoid resistance</td>
</tr>
<tr>
<td></td>
<td>Increase patient’s awareness of the problem and its risks</td>
<td></td>
</tr>
<tr>
<td>Contemplation</td>
<td>Understand patient’s ambivalence and encourage change</td>
<td>Offer opportunity to discuss pros and cons of change using reflective listening</td>
</tr>
<tr>
<td></td>
<td>Build confidence and gain commitment to change</td>
<td></td>
</tr>
<tr>
<td>Preparation</td>
<td>Explore options and choose course most appropriate to patient</td>
<td>Offer realistic options for change and opportunity to discuss inevitable difficulties</td>
</tr>
<tr>
<td></td>
<td>Identify high-risk situations and develop strategies to prevent relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continue to strengthen confidence and commitment</td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>Help patients design rewards for success</td>
<td>Offer positive reinforcement and explore ways of coping with obstacles</td>
</tr>
<tr>
<td></td>
<td>Develop strategies to prevent relapse</td>
<td>Encourage self-rewards to positively reinforce change</td>
</tr>
<tr>
<td></td>
<td>Support and reinforce convictions towards long-term change</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>Help patient maintain motivation</td>
<td>Discuss progress and signs of impending relapse</td>
</tr>
<tr>
<td></td>
<td>Review identified high-risk situations and strategies for preventing relapse</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Help patient view relapse as a learning experience</td>
<td>Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future</td>
</tr>
<tr>
<td></td>
<td>Provide support appropriate to present level of readiness post-relapse</td>
<td>Reassess patient’s readiness to change</td>
</tr>
</tbody>
</table>


Nutrition

General Population
- Key recommendations
  - choose foods that provide more potassium, calcium, vitamin D, and dietary fiber; these include vegetables, fruits, whole grains, and milk/milk products
- Sodium Intake
  - < 2,300 mg/d
  - further reduce intake to <1,500 mg/d in 51+ yr, those of any age who are African American, or have HTN, DM, or CKD (this recommendation applies to about 50% of the US population, including children)
- Fats
  - consume <10% of calories from saturated fatty acids (replace with MUFA and PUFA)
  - consume <300 mg per d of dietary cholesterol
  - limit trans fatty acid consumption (especially synthetic sources of trans fats, such as partially hydrogenated oils)
- Vegetables and Fruits
  - Increase vegetable and fruit intake; favor a variety of vegetables (dark-green, red, and orange), beans, and peas
- Grains
  - consume at least 50% of all grains as whole grains (replace refined grains with whole grains)
- Dairy
  - increase dairy intake overall (milk, yogurt, cheese, or alternatively fortified soy beverages), and favor fat-free or low-fat products
- Proteins
  - eat a variety of protein foods (seafood, lean meat and poultry, eggs, beans/peas, soy products, unsalted nuts/seeds)
  - try to increasingly substitute a variety of seafood in place of meat and poultry
  - replace protein foods that are higher in solid fats with others with a lower solid fat content and/or are a source of oils
- Refined Foods
  - reduce the intake of calories from solid fats and added sugars
  - limit the consumption of refined grain foods that also contain solid fats, added sugars, and sodium

Handy Serving Size Comparisons
- 3 oz meat, fish, poultry → palm of hand
- 1 cup dairy (milk/yogurt) → size of fist
- Bread/grains → one slice, palm of hand
- ½ cup rice/pasta → one hand cupped
- 1 cup of fruit/vegetables → two cupped hands
- 1 oz cheese → full length of thumb
- 1 tsp oil/butter → tip of thumb
- Nuts/chips/snacks → palm covered

Energy Content of Food
- Carbohydrates 4 kcal/g
- Protein 4 kcal/g
- Fat 9 kcal/g
- Ethanol 7 kcal/g

Calculating Total Daily Energy Expenditure (TDEE)
- Roughly 35 kcal/kg/d
- Varies by age, weight, sex, and activity level
- Average 2000-2100 kcal/d for women; 2700-2900 kcal/d for men
**Family Medicine Health Promotion and Counseling**

- recommendations for specific population groups
  - **Women Capable of Becoming Pregnant**
    - choose foods rich in heme iron (more readily absorbed), and enhancers of iron absorption (e.g. vitamin C-rich foods)
    - consume at least 400 µg/d of folic acid (from foods and supplements) in addition to food forms of folate from a varied diet
  - **Pregnant or Breastfeeding Women**
    - consume 8-12 oz of seafood/wk (limit white albacore tuna to 6 oz/wk and do not consume tilefish, shark, swordfish, or king mackerel as they are high in methyl mercury)
    - take an iron supplement if pregnant, as recommended by your healthcare provider
  - **Individuals >50 yr**
    - consume foods fortified in vitamin B12 (e.g. fortified cereals) or use dietary supplements

- counsel on variety, portion size, and plate layout
- vitamins and minerals: see CDC-Vitamins and Minerals, available from: http://www.cdc.gov/nutrition/everyone/basics/vitamins/

### Cardiovascular Disease Prevention

#### Table 3. Dietary Guidelines for Reducing Risk of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fat, Carbohydrates, Protein</strong></td>
<td>Lower LDL</td>
</tr>
<tr>
<td>Overall fat intake: 26-27% of total energy</td>
<td></td>
</tr>
<tr>
<td>Saturated fat: 5-6% of total energy</td>
<td></td>
</tr>
<tr>
<td>Trans fat: reduce intake, replace with MUFA or PUFA</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates: 55-59% of total energy</td>
<td></td>
</tr>
<tr>
<td>Protein: 15-18% of total energy</td>
<td></td>
</tr>
<tr>
<td>Omega-3 Fatty Acid Rich Foods</td>
<td>Decreased sudden death, death from CAD</td>
</tr>
<tr>
<td>≥2 servings/wk of fish (especially oily fish like salmon)</td>
<td></td>
</tr>
<tr>
<td>Salt</td>
<td>Lower TG</td>
</tr>
<tr>
<td>≤2,300 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol</strong></td>
<td>Decreased risk of hypertriglyceridemia, HTN</td>
</tr>
<tr>
<td>≤2 drinks/d for men, ≤1 drink/d for women</td>
<td></td>
</tr>
<tr>
<td><strong>Dietary Approaches</strong></td>
<td>Lower BP, lower LDL</td>
</tr>
<tr>
<td>DASH diet (Dietary Approaches to Stop HTN), recommended by the American Heart Association (AHA)</td>
<td></td>
</tr>
<tr>
<td>Diet: high in vegetables/fruits, low-fat dairy, whole grains, poultry, fish and nuts; Low in sweets, sugar-sweetened beverages, red meats</td>
<td></td>
</tr>
<tr>
<td>Macronutrients: low in saturated/total fat and cholesterol, high in potassium, magnesium, calcium, protein, and fiber</td>
<td></td>
</tr>
</tbody>
</table>

**MUFA** = monounsaturated fatty acids; **PUFA** = polyunsaturated fatty acids

### Obesity

- body mass index (BMI) = weight (kg)/height (m)² = weight (lbs)/height (in)² x 703; BMI is a poor predictor of obesity
- waist circumference (WC) = flexible tape placed on horizontal plane at level of iliac crest
  - should be measured in all adults to assess obesity-related health risks
  - WC measurement for individuals of BMI >35 kg/m² is not necessary (almost all individuals with this BMI will have an abnormal WC)

#### Table 4. Classification of Weight by BMI, Waist Circumference, and Associated Disease Risks in Adults

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Men ≤102 cm (40 in)</th>
<th>Men &gt;102 cm (40 in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased High</td>
</tr>
<tr>
<td>Obesity Class I</td>
<td>30.0-34.9</td>
<td>High</td>
</tr>
<tr>
<td>Obesity Class II</td>
<td>35.0-39.9</td>
<td>Very High</td>
</tr>
<tr>
<td>Obesity Class III (Extreme Obesity)</td>
<td>40.0 +</td>
<td>Extremely High Extremely High</td>
</tr>
</tbody>
</table>


### Adverse Medical Consequences of Obesity

- Type 2 DM
- CAD
- Stroke
- HTN
- Gallbladder disease
- Non-alcoholic steatohepatitis
- Complications of pregnancy
- Dyslipidemia
- Osteoarthritis
- Sleep apnea
- Certain cancers
- CHF
- Low back pain
- Increased total mortality

### Burning Fat

3500 kcal of energy are used for every pound of human fat burned during activity

### Losing Weight

- Aim for caloric intake 500-1000 kcal/d less than total daily energy expenditure (TDEE)
- Results in 1-2 lb (0.5-1 kg) weight loss per wk
- Achieved by combination of increased activity and/or decreased caloric intake

### Low BMI Associations

- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications
Epidemiology
- more than one-third of U.S. adults (34.9%) are obese
- non-Hispanic blacks have the highest age-adjusted rates of obesity (47.8%) followed by Hispanics (42.5%), non-Hispanic whites (32.6%), and non-Hispanic Asians (10.8%)
- obesity is higher among middle age adults, 40-59 yr old (39.5%) than among younger adults, age 20-39 (30.3%) or adults over 60 or above (35.4%) adults
- overweight and obesity rates in children are directly proportional to screen time (see Exercise, FM9)
- only 10-15% of population consume <30% fat daily
- obese persons generally consume more energy-dense food which tends to be highly processed, micronutrient poor, and high in fats, sugars, or starch

AAFP Guidelines For Adults (2012)
- the AAFP recommends screening all adults for obesity; clinicians should offer or refer patients with a BMI of 30 kg/m² or higher to intensive, multicomponent behavioral interventions (Grade B recommendation)
- intensive, multicomponent behavioral interventions include behavioral management activities (12 to 26 sessions in the first yr) such as setting weight loss goals, improving diet/nutrition and increasing physical activity, addressing barriers to change, self-monitoring, and strategizing how to maintain lifestyle changes. For more information: http://www.ahrq.gov/clinic/uspstf10/obeseadult/obesesum.htm

AAFP Guidelines For Children and Adolescents (2010)
- the AAFP recommends that clinicians screen children aged 6 yr and older for obesity and offer them or refer them to comprehensive, intensive behavioral interventions to promote improvement in weight status (Grade B recommendation)
- the definitions for specific interventions (targeted to diet and physical activity) and intensity (>25 h with child and/or family over 6 mo) are noted at: http://www.ahrq.gov/clinic/uspstf10/childobes/chobesrs.htm#clinical

Dyslipidemia
- see Endocrinology, E2
- defined as abnormal elevation of plasma cholesterol or triglyceride levels
- increased risk associated with obesity, DM, alcohol use

Assessment
- measure fasting serum, LDL-C, HDL-C, and TG
- screen with full fasting lipid profile q1-3yr in males >40 yr, females >50 yr or who are menopausal, or any adults with additional CAD risk factors
- assess for presence of other CAD risk factors (smoking, DM, HTN, obesity)
- screen for secondary causes: hypothyroidism, CKD, DM, nephrotic syndrome, liver disease
- risk category
  - estimate using the model for 10 yr CAD risk developed from the Framingham data (Framingham Risk Score – FRS)
  - FRS calculated based on the following factors: gender, age, HDL-C, total cholesterol, sBP, smoking, DM
    - if positive family Hx of CVD in a first degree relative before age 60 then multiply 10 yr CVD risk (%) x 2
    - to be completed for men age 40-75, and women age 50-75 q3-5yr
  - cardiovascular age calculated as patient's age + the difference between his or her estimated remaining life expectancy
    - used to increase adherence to therapy and reaffirm positive effect of following therapy
  - primary target of therapy is LDL-C levels; the alternate primary targets are apolipoprotein B (apo B) and non-HDL-C (not used widely yet)
  - optional secondary targets once LDL-C/apo B is at target include TC: HDL-C ratio, apo B/apo AI ratio, hs-CRP (used more for risk stratification of CAD), non-HDL-C, and serum TG levels
- emerging risk factors (from Framingham group)
  - lipoprotein a
  - metabolic syndrome
  - genetic risk
  - hormone replacement therapy
  - infectious agents

Pharmacotherapy for Obesity
- Orlistat: gastrointestinal lipase inhibitor, reduces fat absorption by 30% by inhibition of pancreatic lipase
- Orlistat is associated with several adverse effects and not approved for clinical use longer than 2 yr
- Orlistat should be avoided in people with inflammatory or chronic bowel disease

Hyperlipidemia Signs
- Atheromatous plaques in blood vessel walls
- Xanthomas: plaques or nodules composed of lipid-laden histiocytes in the skin (especially the eyelids)
- Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
- Corneal arcus (arcus senilis): lipid deposit in cornea
- LDL cannot be calculated when TG ≥4.5 mmol/L

Safety of Statins: An Update
- Therapeutic Advances in Drug Safety 2012;3:133-144
- Trials have shown that statin therapy slightly increases the incidence of DM; however, the absolute risk is small. Relative to the reduction in coronary events, the clinical significance is not great enough to recommend against their use.
Management

- intensity and type of treatment is guided by “risk category” assigned
  1. health behaviors (can decrease LDL-C by up to 10%)
     - smoking cessation: probably the most important for preventing CAD
     - dietary modification: reduce saturated fats, refined sugars, alcohol; increase fruits, vegetables, and fiber
     - physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per week
     - employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high risk patients should start treatment immediately with concurrent health behavior interventions
  2. pharmacologic therapy (can decrease LDL-C by up to 40%)
     - for a comparison of dyslipidemia medications, see Endocrinology, E5
     - statins (HMG-CoA reductase inhibitors)
       - currently recommended as 1st line monotherapy following unsuccessful lifestyle modifications
       - risks: myopathy and hepatotoxicity – must follow LFTs q6-12mo
     - other agents: bile acid sequestrants, niacinic acid, fibrates, cholesterol absorption inhibitors (e.g. ezetimibe)
     - after initiating drug therapy
       - monitor ALT, AST, CK, Cr at baseline then 6 wk later for signs of transaminitis or myositis; tolerate rise in CK up to 10 times upper limit of normal if asymptomatic, or serum creatinine of ≤25%; repeat ALT, AST, and CK with lipid blood work
       - fasting lipids should be measured at 3 mo
     - if adequate response is achieved, evaluate fasting lipids q6-12mo
     - isolated hypertriglyceridemia (does not increase your cardiovascular risk)
       - normal HDL-C and TC, elevated TG
       - mild ≥2.2 mmol/L (≥85 mg/dL); marked ≥5.6 mmol/L (≥217 mg/dL)
       - principal therapy is lifestyle modification
         - weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in diabetics, increased omega-3 fatty acid intake
         - severe hypertriglyceridemia (typically ≥100 mmol/L [≥387 mg/dL]) is associated with an increased risk of acute pancreatitis
     - drug therapy (used to prevent pancreatitis, NOT CVD)
       - nicotinic acid
       - fibrates

Epidemiology

- 25% of the population exercises regularly, 50% occasionally, 25% are sedentary
- screen time (time spent watching TV/movies, playing video games, or using the computer) has been increasing steadily in the last several years, while time spent being physically active has been decreasing
- current recommendation from international pediatric societies is that children (>2 yr old) should limit their screen time to less than 2 h/d
Management

- assess current level of fitness, motivation, and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, DM (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- AAFP recommends that physicians counsel patients to meet recommended levels of physical activity
  - adults: ≥150 min of moderate- to vigorous-intensity aerobic physical activity per wk, or ≥ 75 min of vigorous activity, or an equivalent combination of moderate-to-vigorous activity, in bouts of ≥10 min. For additional benefits, can increase to 300 min of moderate intensity or 150 min of vigorous intensity aerobic physical activity
    - moderate-intensity: brisk walking, bike riding
    - vigorous-intensity: jogging, cross-country skiing
  - children and adolescents: ≥60 min of moderate-to-vigorous-intensity aerobic physical activity daily (with vigorous activity at least 3x wk)
  - older adults (65 yr and older): same as adult guidelines; in addition individuals with poor mobility should perform physical activities to aid with balance and prevent falls
    - when older adults cannot meet the adult guidelines due to chronic illness, they should be as physically active as their abilities and conditions allow
  - every age group: muscle and bone strengthening activities using major muscle groups,
    - adults and older adults: ≥2 d/wk
    - children and adolescents: ≥3d/wk
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, type 2 DM, osteoporosis, and overweight/obesity
  - leads to improved fitness, strength, and mental health (morale and self-esteem)

Smoking Cessation

Epidemiology

- smoking is the single most preventable cause of premature illness and death
- each yr, 440,000 deaths in the US are attributable to smoking or second-hand smoking exposure
- 70% of smokers see a physician each year, but only 28% receive advice or assistance from their physician regarding quitting
- of the 46 million current US smokers, 70% say they would like to quit, but without help only 5% actually quit
- most smokers try to quit on their own (without using evidence-based approaches), and >95% relapse

Management

- general approach
  - the AAFP encourages family physicians to ask about smoking, and then to act to help them quit
  - identify tobacco users; elicit smoking habits, previous quit attempts and results
- AAFP Clinical Preventive Service Recommendation - Tobacco Use
  - clinicians should screen all adults for tobacco use and provide tobacco cessation interventions for those who use tobacco products (Grade A recommendation, 2009)
  - clinicians should screen all pregnant women for tobacco use and provide 5-15 min of smoking cessation counseling using messages and self-help materials tailored for pregnant smokers (Grade A recommendation, 2003)
  - every smoker should be offered treatment
    - combining counseling and smoking cessation medication is more effective than either alone (Grade 1A)
    - individual, phone, and group counseling are effective modalities of counseling (effectiveness increases with treatment intensity); combining two or more components is especially effective
    - make patient aware of withdrawal symptoms
      - low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
    - ≥4 counseling sessions >10 min each with 6-12 mo follow-up yields better results
    - 14% abstinence with counseling vs. 10% without counseling
    - approach depends on patient's stage of change (see Motivational Strategies for Behavioral Change, FM6)
• willing to quit
  • provision of social support, community resources (self-help, group, helpline, web-based strategies)
  • pregnant patients: counseling is recommended as 1st line treatment, as there is insufficient data regarding safety and effectiveness of nicotine replacement therapies (NRT) in this population

• pharmacologic therapy
  1. nicotine replacement therapy
     • 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
     • no difference in achieving abstinence for different forms of NRT
     • reduces cravings and withdrawal symptoms without other harmful substances that are contained in cigarettes
     • use with caution: immediate post-MI, serious/worsening angina, serious arrhythmia
     • advise NO smoking while using NRT
  2. antidepressants (note: mode of action appears to be independent of antidepressant effect)
     • Bupropion SR (Zyban*)
       • 21% abstinent at 12 mo vs. 8% for placebo
       • no advantage for NRT vs. bupropion (similarly effective)
     • Nortriptyline (2nd line, not officially approved for smoking cessation)
       • effectiveness comparable to bupropion
  3. Varenicline (Champix®)
     • partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce the response to smoked nicotine)
     • more effective than bupropion (23% abstinent from 9-52 wk with varenicline vs. 16% for bupropion vs. 9% with placebo)

Table 7. Pharmacologic Treatments for Smoking Cessation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Dosage</th>
<th>Prescribing*</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| Bupropion          | Inhibits re-uptake of dopamine and/or noradrenaline, competitive antagonist of norepinephrine | 1. 150 mg qAM x 3 d
                       |                                                | 2. Then 150 mg bid x 7-12 wk
                       |                                                | 3. For maintenance consider 150 mg bid for up to 6 mo         | Seizure disorder
|                    |                                                | 1. Decide on a quit date
                       |                                                | 2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk) | Eating disorder
|                    |                                                | 3. Then 12 wk therapeutic dose of 70-100 mg daily                  | Simultaneous use of MAOI use in past 14 d | Major depression
| Nortriptyline (2nd line) | Inhibits adrenergic re-uptake (may also inhibit serotonin/histamine re-uptake) | 1. Initial titration before the quit attempt (10-20 d)
                       |                                                | 2. Then 12 wk therapeutic dose of 70-100 mg daily                  | Usually prescribed when 1st line treatments have been unsuccessful | Acute recovery period following MI
|                    |                                                | 3. Continue to smoke for first wk of treatment and then completely stop (therapeutic levels reached in 1 wk) | MAOI use in past 14 d | Following MI
| Varenicline        | Partial nicotinic receptor agonist, and partial nicotinic receptor competitive antagonist | 1. 0.5 mg qAM x 3 d
                       |                                                | 2. Then 0.5 mg bid x 4 d
                       |                                                | 3. Then 1 mg bid x 12 wk ± additional 12 wk as maintenance       | Caution with pre-existing psychiatric condition

Table 6. Types of Nicotine Replacement Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Dosage</th>
<th>Comment</th>
<th>Side Effects</th>
</tr>
</thead>
</table>
| Nicotine Gum (OTC)  | 2 mg if < 25 cig/d
                       | 4 mg if > 25 cig/d
                       | 1 piece q1-2h for 1-3 mo (max 24 pieces/d)  | Chew until “peppery” taste then “park” between gum and cheek to facilitate absorption
                       | Continue to chew park intermittently for 30 min | Mouth soreness, Hiccups, Dyspepsia, Jaw ache
| Nicotine Patch (OTC)| Use for 8 wk
                       | 21 mg/d x 4 wk
                       | 14 mg/d x 2 wk
                       | 7 mg/d x 2 wk                             | Start with lower dose if < 10 cig/d
                       | Change patch q24h and alternate sides      | Skin irritation, Insomnia, Palpitations, Anxiety
| Nicotine Inhaler (OTC)| 6-16 cartridges/d
                           | for up to 12 wk                             | Nicotine inhaled through mouth, absorbed in mouth and throat not in lungs | Local irritation, Coughing
| Nicotine Nasal Spray (Rx)| Never form of NRT                     | Nevers form of NRT                           | Local irritation, coughing

*May be used in combination with nicotine replacement therapy.
unwilling to quit

- motivational intervention (5 Rs)
  1. Relevance to patient
     - relevant to patient's disease status or risk, family or social situation (e.g. having children in the home), health concerns, age, gender
  2. Risks of smoking
     - short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
     - long-term: MI, stroke, COPD, lung CA, other cancers
     - environmental: higher risk in spouse/children for lung CA, SIDS, asthma, respiratory infections
  3. Rewards: benefits
     - improved health, save money, food tastes better, good example to children
  4. Roadblocks: obstacles
     - fear of withdrawal, weight gain, failure, lack of support
  5. Repetition
     - reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)
  - recent quitter
     - highest relapse rate within 3 mo of quitting

- recent quitter

- minimal practice: congratulate on success, encourage ongoing abstinence, review benefits and problems

Alcohol

- see Psychiatry, PS19

Definition
- diagnostic categories occur along a continuum

Epidemiology
- 10-15% of patients in family practice are problem drinkers
- more likely to miss diagnosis in women or elderly patients with high socioeconomic status

Assessment
- screen for alcohol dependence with CAGE questionnaire
  - if CAGE positive, explore with further questions for alcohol abuse/dependence
- assess drinking profile
  - setting, time, place, occasion, with whom
  - impact on: family, work, social
  - quantity-frequency history
    - how many drinks per d?
    - how many days per wk?
    - maximum number of drinks on any 1 d in the past month?
  - if identified positive for alcohol problem
    - screen for other drug use
    - identify medical-psychiatric complications
    - ask about drinking and driving
    - ask about past recovery attempts and current readiness for change

Investigations
- GGT and MCV for baseline and follow-up monitoring
- AST, ALT (usually AST:ALT approaches 2:1 in an alcoholic)
- CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by liver)

Management
- intervention should be consistent with patient's motivation for change
- regular follow-up is crucial
- 10% of patients in alcohol withdrawal will have seizures or delirium tremens
- Alcoholics Anonymous/12-steps program
- outpatient/day programs for those with chronic, resistant problems
- family treatment (Al-Anon, Alateen, screen for spouse/child abuse)
- in-patient program if
  - dangerous or highly unstable home environment
  - severe medical/psychiatric problem

- standard drink equivalents
  - one standard drink = 14 g of pure alcohol
    - Beer (5% alcohol) = 12 oz
    - Wine (12-17% alcohol) = 5 oz
    - Fortified wine = 3 oz
    - Hard liquor (40%) = 1.5 oz

- CAGE questionnaire
  - C Have you ever felt the need to CUT down on your drinking?
  - A Have you ever felt ANNOYED at criticism of your drinking?
  - G Have you ever felt GUILTY about your drinking?
  - E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (EYE OPENER)

  - ≥2 for men or ≥1 for women suggests possibility of problem drinking (sensitivity 85%, specificity 89%)

- some adverse medical consequences of problem drinking
  - GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/oesophageal cancer
  - Cardiac: HTN, alcoholic cardiomyopathy
  - Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
  - Hematologic: anemia, coagulopathies
  - Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage
• addiction to drug that may require in-patient detoxification
• refractory to other treatment programs
  • pharmacologic
    • diazepam for withdrawal
    • disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, N/V, hypotension if alcohol is ingested
    • naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
      • may trigger withdrawal in opioid-dependent patients

**Prognosis**
• relapse is common and should not be viewed as failure
• monitor regularly for signs of relapse
• 25-30% of abusers exhibit spontaneous improvement over 1 yr
• 60-70% of individuals with jobs and families have an improved quality of life 1 yr post-treatment

---

### Common Presenting Problems

#### Abdominal Pain

• see Gastroenterology, G4 and General Surgery, GS4

**Epidemiology**
• 20% of individuals have experienced abdominal pain within the last 6-12 mo
• 90% resolve in 2-3 wk
• only 10% are referred to specialists, of those <10% admitted to hospital

**Etiology**
• most common diagnosis is “nonspecific abdominal pain,” which has no identifiable cause and is usually self-limited
• GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
• urinary tract disorders (e.g. UTI, renal calculi)
• gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
• cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
• other: medications (e.g. NSAIDs), alcohol, toxic ingestion, foreign body, psychogenic

**Pathophysiology**
• type of pain
  • somatic pain: sharp, localized pain
  • visceral pain: dull, generalized pain
• location of pain
  • epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
  • periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon
  • hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region

**Investigations**
• guided by findings on history and physical
• possible blood work: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, tox screen, β-hCG
• imaging
  • CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  • abdominal x-ray, KUB (consider: gas pattern, free air, kidney stones, constipation)
  • ultrasound (gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  • CT scan (AAA, appendicitis)
• other tests
  • urinalysis
  • endoscopy (for peptic ulcers, gastritis, tumors, etc.)
  • *H. pylori* testing (urea breath test, serology, biopsy)

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**Key Definitions for Alcohol**

**What is moderate alcohol consumption?** Moderate alcohol consumption is defined as up to 1 drink per d for women and up to 2 drinks per d for men.

**What is heavy or high-risk drinking?** Heavy or high-risk drinking is the consumption of more than 3 drinks on any day or more than 7 wk for women and more than 4 drinks on any day or more than 14 per wk for men.

**What is binge drinking?** Binge drinking is the consumption within 2 h of 4 or more drinks for women and 5 or more drinks for men.

Allergic Rhinitis

- see Otolaryngology, OT24

**Definition**
- inflammation of the nasal mucosa that is triggered by an allergic reaction

**Classification**
- seasonal
  - symptoms during a specific time of the year
  - common allergens: trees, grass and weed pollens, airborne molds
- perennial
  - symptoms throughout the year with variation in severity
  - common allergens: dust mites, animal dander, molds

**Etiology**
- increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

**Epidemiology**
- affects approximately 40% of children and 20-30% of adults
- prevalence has increased in developed countries, particularly in the past two decades
- associated with asthma, eczema, sinusitis, and otitis media

**Assessment**
- identify allergens
- take an environmental/occupational history
- ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

**Management**
- conservative
  - minimize exposure to allergens
  - most important aspect of management, often sufficient (may take months)
  - maintain hygiene, saline nasal rinses
- pharmacologic agents
  - oral antihistamines – first line therapy for mild symptoms
    - e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  - intranasal corticosteroids for moderate/severe or persistent symptoms (>1 mo of consistent use to see results)
  - intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)
- allergy skin testing
  - reserved for severe cases unresponsive to pharmacologic agents
  - consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

Amenorrhea

- see Gynecology, G9

Anxiety

- see Psychiatry, PS10

**Epidemiology**
- 25-30% of patients in primary care settings have psychiatric disorders
- many are undiagnosed or untreated; hence the need for good screening
- high rate of coexistence of anxiety disorders and depression

**Screening**
- screening questions
  - Do you tend to be an anxious or nervous person?
  - Have you felt unusually worried about things recently?
  - Has this worrying affected your life? How?
Asthma/COPD

**Definition**

- **asthma**
  - chronic but reversible airway inflammation characterized by periodic attacks of wheezing, SOB, chest tightness, and coughing
  - airways hyper-responsive to triggers/antigens leading to acute obstructive symptoms by bronchoconstriction, mucous plugs, and increased inflammation
  - cannot be diagnosed at first presentation; called reactive airway disease until recurrent presentations
  - pulmonary function tests (PFTs) can be done from age 6 or when child able to follow instructions to do PFTs
  - peak flow meters are useful in the office and at home for monitoring
  - chronic obstructive pulmonary disease (COPD)
    - a group of chronic, progressive, expiratory lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
    - emphysema and chronic bronchitis are the most common forms of COPD

**Assessment**

- associated symptoms
- risk factors
  - family history of anxiety or depression, past history of anxiety, stressful life event, social isolation, female, comorbid psychiatric diagnosis (e.g. depression)
- assess substance abuse, comorbid depression, stressful life events, trauma, suicidal ideation/self-harm
- to differentiate anxiety disorders, consider symptoms (panic attacks, specific situations/stressors, excessive worry about common concerns, repetitive thoughts and/or behaviors to neutralize the anxiety) and their duration

**Management**

- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- lifestyle advice: decrease caffeine and alcohol intake, exercise, relaxation techniques, mindfulness strategies
- self-help materials, community resources (e.g. support groups)
- CBT: cognitive interventions, exposure therapy, etc.
- provide support to family and caregivers
- for pharmacotherapy, see Psychiatry, PS47

**Rule Out**

- Cardiac (post MI, arrhythmias)
- Endocrine (hyperthyroidism, DM, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatoform disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (OCPD)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/benzodiazepine withdrawal)

**Differential Diagnosis of Anxiety Disorders**

- Panic disorder
- GAD
- Social Anxiety Disorder (previously Social Phobia)
- Agoraphobia
- Specific phobia
- Selective Mutism
- Separation Anxiety Disorder
- Other: AMC, mood disorder, psychotic disorder, OCD, PTSD

**Symptoms of GAD**

- Anxious, nervous, or worried
- No control over the worry
- Duration > 6 mo
- Irritability
- Concentration impairment
- Restlessness
- Energy decreased
- Sleep impairment
- Tension in muscles

**Table 8. Differentiating COPD from Asthma**

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>Usually in 6th decade</td>
</tr>
<tr>
<td>Role of Smoking</td>
<td>&gt;10 pack yr</td>
</tr>
<tr>
<td>Reversibility of Airflow Obstruction</td>
<td>Airflow obstruction is chronic and persistent</td>
</tr>
<tr>
<td>Evolution</td>
<td>Slow, progressive worsening (with periodic exacerbations)</td>
</tr>
<tr>
<td>History of Allergy</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Precipitators</td>
<td>Environmental irritants (air pollution), cigarette smoking, α-1 antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs)</td>
</tr>
<tr>
<td>Symptoms/Signs</td>
<td>Chronic cough, sputum, and/or dyspnea</td>
</tr>
<tr>
<td>Diffusion Capacity</td>
<td>Decreased (more so in pure emphysema)</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>Chronic in advanced stages</td>
</tr>
<tr>
<td>Spirometry</td>
<td>May have improvement with bronchodilators but not universally seen</td>
</tr>
</tbody>
</table>

**Signs of Poorly Controlled Asthma**

- Inh agonist use >4x/wk
- Asthma-related absence from work/school
- Exercise induced asthma
- Night-time symptoms >1x/wk

**Figure 3. Expiratory flow volume curves (obstructive, normal, and restrictive disease)**

- Normal
- Obstructive
- Restrictive
- LUNG VOLUME (L)
- FLOW RATE (L/sec)
- VC, FEV1, FEF25-75%
- Normal curve, obstructive curve, restrictive curve
- One second time marker

Benign Prostatic Hyperplasia

- ser{}um PSA: protein produced by prostatic tissue, see Urology, U25
- urinalysis to exclude UTI and for microscopic hematuria (common sign)

### Investigations
- urinalysis to exclude UTI and for microscopic hematuria (common sign)
- serum PSA: protein produced by prostatic tissue, see Urology, U25
  - values
    - <4.0 ng/mL: normal, but must take into account patient’s age and velocity of PSA increase
    - 4-10 ng/mL: consider measuring free/total PSA
    - >10 ng/mL: high likelihood of prostate pathology
- PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI
- increased PSA in a younger man is more often due to cancer than other causes
- abnormal DRE or PSA should trigger further assessment
- decision to test PSA in an asymptomatic man should involve discussion about the risks and possible benefits
- other tests
  - Cr, BUN
  - post-void residual volume by ultrasound
  - renal ultrasound
  - patient voiding diary
- tests NOT recommended as part of routine initial evaluation include
  - cystoscopy
  - cytology
  - prostate ultrasound or biopsy
  - IVP
  - urodynamic studies

### Management

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest X-Ray</strong></td>
<td>Often normal</td>
</tr>
<tr>
<td>Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist, bullae</td>
<td>Hyperinflation during asthma attack</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Ongoing patient education, and environmental control</td>
</tr>
<tr>
<td>Step 1: SABA pm (salbutamol)</td>
<td>SABA taken pm as rescue medication + maintenance meds</td>
</tr>
<tr>
<td>Step 2: SABA pm + LAAC (i.e. tiotropium) or LABA (e.g. salmeterol)</td>
<td>Maintenance medications:</td>
</tr>
<tr>
<td><strong>Severe</strong></td>
<td>Step 1: Low-dose ICS</td>
</tr>
<tr>
<td>Step 3: SABA pm + LAAC + low-dose combined ICS/LABA; consider inhaled vs. oral steroids</td>
<td>Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LT modifier, or long-acting theophylline</td>
</tr>
<tr>
<td>Step 4: ± theophylline</td>
<td>Step 3: Medium/high-dose ICS plus either LABA, LT modifier, or long-acting theophylline</td>
</tr>
<tr>
<td>Pneumococcal vaccination, annual influenza immunization</td>
<td>Step 4: As above plus immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization</td>
</tr>
</tbody>
</table>

LAAC = long-acting anticholinergic; LABA = long-acting β-agonist; LT modifier = leukotriene modifier; SABA = short-acting β-agonist

<table>
<thead>
<tr>
<th>What Color is Your Inhaler?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
</tr>
<tr>
<td>β- Agonists</td>
</tr>
<tr>
<td>Salbutamol – Ventolin®</td>
</tr>
<tr>
<td>Salmeterol – Serevent®</td>
</tr>
<tr>
<td>Terbutaline – Bricanyl®</td>
</tr>
<tr>
<td>ICS</td>
</tr>
<tr>
<td>Fluticasone – Flovent®</td>
</tr>
<tr>
<td>Budesonide – Pulmicort®</td>
</tr>
<tr>
<td>Combined Long-Acting β-Agonist + ICS</td>
</tr>
<tr>
<td>Fluticasone/Salmeterol – purple discus</td>
</tr>
<tr>
<td>Budesonide/Formoterol – red/white</td>
</tr>
<tr>
<td>Ipratropium/Albuterol – clear/orange</td>
</tr>
<tr>
<td>Tiotropium Albuterol – Combivent®</td>
</tr>
<tr>
<td>Anticholinergics</td>
</tr>
<tr>
<td>Ipratropium – Atrovent®</td>
</tr>
<tr>
<td>Tiotropium – Spiriva®</td>
</tr>
</tbody>
</table>

### More About Inhalers
- Aerosols (puffers=MDI, MDI + spacer) MDIs should be used with spacers to:
  - Reduce side effects
  - Improve amount inhaled
  - Increase efficiency of use
- Dry Powder Inhaler (discus, turbuhaler and diskhaler), they require deep and fast breathing (may not be ideal for children)
- Nebulizers can be used to convert liquid medications into a fine mist; recommended for use if contraindications to MDIs

### Differential Diagnosis of Wheezing
- Allergies, anaphylaxis
- Asthma, reactive airway disease
- GERD
- Infections (bronchitis, pneumonia)
- Obstructive Sleep Apnea
- COPD
- Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction

### Self-Management Asthma and COPD Education and Written Action Plan
- Education is a key component in management of asthma and COPD
- Guided self-management combining education, regular medical review, self-assessment, and written action plan have been shown to reduce hospitalizations, ED visits, and missed days at work or school
- Sample action plans available online: http://www.respiratoryguidelines.ca

### More About Asthma
- Leukotrienes (LTD4, LTE4, LTB4)
- *Lowering of the threshold for bronchial smooth muscle to spasmogen (contracting agent) or mediator (chemical substance)*

### More About COPD
- Tiotropium – Spiriva®
- Ipratropium/Albuterol – Combivent®
- Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist, bullae
- COPD
- Obstructive Sleep Apnea
- Infections (bronchitis, pneumonia)
- GERD
- Asthma, reactive airway disease
- Allergies, anaphylaxis

### When prescribing salbutamol, watch out for signs of hypokalemia: lethargy, irritability, paresthesias, myalgias, weakness, palpitations, N/V, polyuria

### Table 8. Differentiating COPD from Asthma (continued)

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Management</strong></td>
<td>Ongoing patient education, and environmental control</td>
</tr>
<tr>
<td>Mild</td>
<td>SABA taken pm as rescue medication + maintenance meds</td>
</tr>
<tr>
<td>Moderate</td>
<td>Maintenance medications:</td>
</tr>
<tr>
<td>Severe</td>
<td>Step 1: Low-dose ICS</td>
</tr>
<tr>
<td>Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LT modifier, or long-acting theophylline</td>
<td></td>
</tr>
<tr>
<td>Step 3: Medium/high-dose ICS plus either LABA, LT modifier, or long-acting theophylline</td>
<td></td>
</tr>
<tr>
<td>Step 4: As above plus immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization</td>
<td></td>
</tr>
</tbody>
</table>

LAAC = long-acting anticholinergic; LABA = long-acting β-agonist; LT modifier = leukotriene modifier; SABA = short-acting β-agonist
Table 9. Symptoms and Complications of BPH

<table>
<thead>
<tr>
<th>Obstructive Symptoms</th>
<th>Irritative Symptoms</th>
<th>Late Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesitancy (difficulty starting urine flow)</td>
<td>Urgency</td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Diminution in size and force of urinary stream</td>
<td>Frequency</td>
<td>Loss of renal concentrating ability</td>
</tr>
<tr>
<td>Stream interruption (double voiding)</td>
<td>Urgine incontinence</td>
<td>Systemic acidosis</td>
</tr>
<tr>
<td>Urinary retention (bladder does not feel completely empty)</td>
<td>Dysuria</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Post-void dribbling</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overflow incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management

- referral to urologist if moderate/severe symptoms
- conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
  - fluid restriction (avoid alcohol and caffeine)
  - avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
  - pelvic floor/Kegel exercises
  - bladder retraining (scheduled voiding)
- pharmacological: for moderate/severe symptoms
  - $\alpha$-receptor antagonists (e.g. terazosin [Hytrin®], doxazosin [Cardura®], tamsulosin [Flomax®], alfuzosin [Xatral®])
    - relaxation of smooth muscle around the prostate and bladder neck
  - 5-alpha reductase inhibitor (e.g. finasteride [Proscar®])
    - only for patients with demonstrated prostatic enlargement due to BPH
    - inhibits enzyme responsible for conversion of testosterone into dihydrotestosterone (DHT) thus reducing growth of prostate
  - phytotherapy (e.g. saw palmetto berry extract, Pygeum africanum)
    - more studies required before this can be recommended as standard therapy
  - considered safe
- surgical
  - TURP (transurethral resection of the prostate), TUİP (transurethral incision of the prostate, for prostates <30 g)
  - absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
  - complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido

Bronchitis (Acute)

Definition

- acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

Epidemiology

- 5th most common diagnosis in family medicine, most common is URTI

Etiology

- 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV)
- 20% bacterial: M. pneumoniae, C. pneumoniae, S. pneumoniae

Investigations

- acute bronchitis is typically a clinical diagnosis
- sputum culture/gram stain is not very informative
- CXR if suspect pneumonia (cough >3 wk, abnormal vital signs, localized chest findings) or CHF
- PFT with methacholine challenge if suspect asthma

Management

- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids (3-4 L/d when febrile), humidity, analgesics and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
- antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic (see Antimicrobial Quick Reference, FM53)
- antibiotics in children show no benefit
**Chest Pain**

- see Cardiology and Cardiac Surgery, C4 and Emergency Medicine, ER21

**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>GI</th>
<th>Musculoskeletal/Neuro</th>
<th>Psychologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic dissection*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pericarditis*</td>
<td>Pulmonary HTN</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Emergent

**Investigations**

- ECG, CXR, and others if indicated (cardiac enzymes, d-dimers, liver function tests [LFTs], etc.)
- refer to ED if suspect serious etiology (e.g. aortic dissection, MI)

**Management of Common Causes of Chest Pain**

- angina/ischemic heart disease
  - nitroglycerin (NTG): wait 5 min between sprays and if no effect after 3 sprays, send to ED
  - myocardial infarction
    - ASA (160-325 mg, chewed stat), clopidogrel (Plavix®), LMWH (enoxaparin), morphine, oxygen, NTG
    - ± reperfusion therapy with fibrinolytics (e.g. tPA, RPA, TNK, or SK) if within 12 h (ideally <30 min) or percutaneous intervention (cath lab) if <90 min
    - start β-blocker (e.g. metoprolol starting dose 25 mg PO q6h or bid, titrating to HR goal of 55-60 bpm)
- endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results
- GERD: antacids, H2 blockers, PPIs, patient education
- costochondritis: NSAIDs

**Treatment of Stable Ischemic Heart Disease**

- see Cardiology and Cardiac Surgery, C26

---

**Common Cold (Acute Rhinitis)**

- see Infectious Diseases, ID8 (Pneumonia and Influenza)

**Definition**

- viral URI with inflammation

**Epidemiology**

- most common diagnosis in family medicine, peaks in winter months
- incidence: adults = 2-4/yr, children = 6-10/yr
- organisms
  - mainly rhinoviruses (30-35% of all colds)
  - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
- incubation: 1-5 d
- transmission: person-person contact via secretions on skin/objects and by aerosol droplets

**Risk Factors**

- psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

**Clinical Features**

- symptoms
  - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
  - general: malaise, headache, myalgias, mild fever
- signs
  - boggy and erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam

---

**Influenza vs. Colds: A Guide to Symptoms**

<table>
<thead>
<tr>
<th>Features</th>
<th>Flu</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Illness</td>
<td>Sudden</td>
<td>Slow</td>
</tr>
<tr>
<td>Fever</td>
<td>High fever</td>
<td>None</td>
</tr>
<tr>
<td>Exhaustion level</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Cough</td>
<td>Dry severe</td>
<td>=</td>
</tr>
<tr>
<td>or hacking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Throat</td>
<td>Free</td>
<td>Sore</td>
</tr>
<tr>
<td>Nose</td>
<td>Dry and clear</td>
<td>Runny</td>
</tr>
<tr>
<td>Head</td>
<td>Achy</td>
<td>Headache-free</td>
</tr>
<tr>
<td>Appetite</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Muscles</td>
<td>Achy</td>
<td>Fine</td>
</tr>
<tr>
<td>Chills</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
• complications
  ▪ secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
  ▪ asthma/COPD exacerbation

Differential Diagnosis
• allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

Management
• patient education
  ▪ symptoms peak at 1-3 d and usually subside within 1 wk
  ▪ cough may persist for days to weeks after other symptoms disappear
  ▪ no antibiotics indicated because of viral etiology
  ▪ secondary bacterial infection can present within 3-10 d after onset of cold symptoms
• prevention
  ▪ frequent hand washing, avoidance of hand to mucous membrane contact, use of surface disinfectant
  ▪ yearly influenza vaccination
• symptomatic relief
  ▪ rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
  ▪ analgesics and antipyretics: acetaminophen, ASA (not in children because of risk of Reye’s syndrome)
  ▪ cough suppression: dextromethorphan or codeine if necessary (children under 6 yr of age should not use any cough/cold medications)
  ▪ decongestants, antihistamines
  ▪ zinc lozenge use may help to reduced the duration of cold symptoms
• patients with reactive airway disease will require increased use of bronchodilators and inhaled steroids

Contraception

Table 11. Methods of Contraception

<table>
<thead>
<tr>
<th>Methods</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined OCP (e.g. Alesse®, Tr-Conyle®)</td>
<td>99.9% effective with perfect use, 97-99% with typical use, cycle control, ↓ dysmenorrhea, ↓ menstrual flow, ↓ ovarian cancer, ↓ endometrial cancer, ↓ risk of fibroids, ↓ acne, ↓ hirsutism</td>
<td>Irregular bleeding, systemic hormonal side effects (breast tenderness, nausea, mood changes), no STD protection, slightly increased risk of venous thromboembolism (VTE), MI, stroke, decreased quantity of breast milk postpartum</td>
</tr>
<tr>
<td>Progestin Only Pill (e.g. Micronor®)</td>
<td>At least 95% effective with perfect use, no increased risk of VTE, MI, or stroke, suitable for postpartum</td>
<td>Hormonal side effects (see Combined OCP)</td>
</tr>
<tr>
<td>Transdermal Patch (e.g. Evra®)</td>
<td>Same as OCP, easy to use, changed weekly, 99% effective with correct use</td>
<td>Same as OCP, skin irritation</td>
</tr>
<tr>
<td>Nuvapril® (inserted by patient)</td>
<td>Same as OCP, easy to use (in for 3 wk, out for 1 wk), less systemic hormonal side effects, 99% effective with correct use</td>
<td>Same as OCP, vaginitis, some women may be uncomfortable with self-insertion</td>
</tr>
<tr>
<td>DMPA IM progesterone injection q12wk (e.g. DepoProvera®)</td>
<td>99.7% effective against pregnancy, infrequent dosing, ↓ menstrual flow or amenorrhea, ↓ risk of endometrial cancer</td>
<td>Irregular bleeding, delayed return of fertility, no STD protection, systemic hormonal side effects (most common is headache), weight gain, ↓ bone mineral density (check after 5 yr)</td>
</tr>
<tr>
<td>Male Condom</td>
<td>97% effective against pregnancy and STDs when used properly; when used properly WITH spermicide they are close to 99.9% effective, no Rx required</td>
<td>Latex allergy, irritation, only effective before the expiry date, must be applied properly, can only be used once</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>92-96% effective with perfect use, non-hormonal, female-controlled method of contraception, ↓ risk of cervical cancer</td>
<td>Must be left in for 6 h after intercourse, must be used with spermicide, incomplete STD protection, latex allergy, must be fitted by health care worker, ↑ risk of UTI, risk of toxic shock syndrome</td>
</tr>
<tr>
<td>Sponge</td>
<td>One-size-fits-all barrier method, does not require fitting by MD, available in pharmacies, 90% effective without a condom, 98% effective with a condom</td>
<td>Relatively expensive, only ~60% effective in parous women, incomplete STD protection, risk of toxic shock syndrome</td>
</tr>
</tbody>
</table>

Concussion/Mild Traumatic Brain Injury

• see Neurosurgery, NS29, and Emergency Medicine, ER7
• a useful tool for the assessment of individuals and athletes with concussion is the Sport Concussion Assessment Tool, 3rd edition (SCAT3), Br J Sports Med 2013;47:259

Zinc for the Treatment of the Common Cold: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

CMAJ 2012;184:E551-561
Study: Meta-analysis of 17 randomized control trials with a total of 2,121 participants.
Patients: All populations.
Intervention: Orally administered zinc vs. placebo or no treatment.
Results: Patients receiving zinc had a shorter duration of cold symptoms compared with those given placebo (mean difference -1.65 d). Zinc shortened the duration of symptoms in adults but no significant difference was seen in children. Adverse events such as nausea were more common in the zinc group (RR 1.640).

Echinacea for Preventing and Treating the Common Cold

Cochrane DB Syst Rev 2014;2:CD000530
This systematic review of 24 trials assessed the effect of Echinacea in preventing and treating common colds. Trials compared preparations containing Echinacea with placebo, no treatment, or an alternative common cold treatment.
Conclusions: Echinacea products have not been shown to provide benefits for treating colds, although, it is possible there is a weak benefit from some Echinacea products. Individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance.
### Table 11. Methods of Contraception (continued)

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrauterine Device (IUD)</td>
<td>99% effective against pregnancy, effective for 5 yr, no daily regimen required, can be easily removed, ideal in post-partum women</td>
<td>No STD protection, † relative risk of PID in first mo, must be inserted by MD, risk of post-insertion vaso-vegal response, risk of uterine rupture is 0.6-1.6/1,000, 2-10% expulsion rate</td>
</tr>
<tr>
<td>Levonorgestrel (e.g., Mirena®)</td>
<td>Spotting, less systemic hormonal side effects than OCP</td>
<td>Hormonal side effects are possible with levonorgestrel IUD, but less than OCP (see combined OCP), expensive (~$400)</td>
</tr>
<tr>
<td>Copper IUD (e.g., Nova T®)</td>
<td>↓ risk of endometrial cancer, less expensive than Mirena (~$170)</td>
<td>Irregular bleeding or ↑ menstrual flow with copper IUD, 6-20% women discontinue use in first 5 yr because of pain or ↑ bleeding</td>
</tr>
<tr>
<td>Fertility Awareness/ Natural Family Planning (e.g., symptothermal method)</td>
<td>Effectiveness: 95-98% with perfect use, 75-88% with typical use, increased awareness of gynecological health, reasonable for couples for whom an unplanned pregnancy would be acceptable</td>
<td>High probability of failure if not used consistently and correctly, no STD protection</td>
</tr>
<tr>
<td>Lactational Amenorrhea</td>
<td>Can be effective in breastfeeding women if menses not returned, fully or nearly fully breastfeeding baby and baby is under 6 mo old</td>
<td>Not effective if infant receives any food supplementary to breastfeeding Must breastfeed regularly, even through the night (at least q6h) Most effective is breastfeeding q2-3h</td>
</tr>
</tbody>
</table>

### EMERGENCY CONTRACEPTION
- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 h apart) or post-coital IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
- post-coital IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%) |
- pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
- advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
- pharmacists across Canada can dispense Plan B® OTC

### Cough

**History and Physical**
- duration (chronic - 8 wk), onset, frequency, quality (dry vs. productive), sputum characteristics, provoking/relieving factors, recent changes
- associated symptoms: fever, dyspnea, hemoptysis, wheezing, chest pain, orthopnea, PND, rhinitis, reflux, post-nasal drip
- constitutional symptoms: fever, chills, fatigue, night sweats
- risk factors: smoking, occupation, exposure, family history of lung CA or other CA, TB status, recent travel
- medications (e.g. ACEI, β-blockers), allergies
- PMH: lung (asthma, COPD, CF), heart (CHF, MI, arrhythmias), chronic illness, GI (reflux)  
- vitals including O₂ saturation, respiratory exam, HEENT and precordial exam

**Investigations**
- guided by findings on history and physical
  - consider throat swab, CXR, PFTs, upper GI series, sputum culture test for acid-fast bacilli (if TB is suspected)

### Dementia (Major Neurocognitive Disorder)

- see Psychiatry, PS17

**Epidemiology**
- 10% in patients over the age of 65, 25% in patients over the age of 85, 50% in patients over the age of 90
- prevalence increases with age, Down syndrome, and head trauma
- differential diagnosis: Alzheimer’s dementia, vascular dementia, Lewy-Body dementia, frontotemporal dementia

**Investigations**
- history, physical exam, MMSE, MOCA (best screening test), dementia quick screen (see sidebar)
- investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
- CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin B₁₂, folate, VDRL, HIV, head CT
Management

- Treat and prevent reversible causes
- Provide orientation cues (e.g., calendars, clocks) and optimize vision and hearing
- Family education, counseling, and support (respite programs, group homes)
- Pharmacologic therapy: NMDA receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose neuroleptics and antidepressants can be used to treat behavioral and emotional symptoms
- 20% of patients develop clinical depression, most commonly seen in vascular dementia

Depression

- See Psychiatry, PS6

Etiology

- Often presents as non-specific complaints (e.g., sleep disturbance, chronic fatigue, pain)
- Depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
- 2/3 of depressed persons may not receive appropriate treatment for their depression
- Identification and early treatment improve outcomes

Screening Questions

- The AAFP recommends screening adults for depression when staff-assisted depression care supports are available (Grade B)
- “Staff-assisted depression care supports” refers to clinical staff that assist the primary care physician in providing direct depression care and/or coordination, case management, or mental health treatment
- If staff-assisted depression care supports are not available, the AAFP recommends against routine screening of adults (Grade C) (note: there may be considerations that support screening for depression in an individual patient)
  - “Are you depressed?” (high specificity and sensitivity)
  - “Have you lost interest or pleasure in the things you usually like to do?” (anhedonia)
  - “Do you have problems sleeping?”
- For geriatric population, use the Geriatric Depression Scale (GDS) short form for screening

Assessment

- Risk factors: see Psychiatry, PS7
- Personal or family history of depression
- Medications and potential substance abuse problems
- High risk suicidality/homicidality
  - Fill out Form 1 (in Ontario): application by physician to hospitalize a patient against his/her will for psychiatric assessment (up to 72 h)
  - Functional impairment (e.g., work, relationships)
- At least 5 out of 9 criteria including at least one of anhedonia or depressed mood ≥2 wk for actual diagnosis to be met (see sidebar)
- Validated depression rating scales: Beck’s depression inventory, Zung’s self-rating depression scale, Children’s depression inventory, Geriatric Depression Scale, Personal Health Questionnaire Depression Scale (PHQ-9)
- Routine medical workup (physical exam, CBC, TSH, ferritin, folate, B12, electrolytes, urinalysis, glucose, etc.)

Treatment

- Goal: full remission of symptoms and return to baseline psychosocial function
- Phases of treatment
  - Acute phase (8-12 wk): relieve symptoms and improve quality of life
  - Maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
  - Treatment can consist of pharmacotherapy alone or psychotherapy alone
  - Combination of antidepressant drug therapy and psychotherapy results in synergistic effects
  - Treatment of youth (age 10-21)
    - For mild depression, a period of active support and monitoring before initiating treatment is recommended
    - Fluoxetine is first line among SSRIs (most evidence)
    - Monitor closely for adverse effects such as suicidal ideation and behavior
    - Psychotherapy
      - CBT or interpersonal therapy (IPT) alone can be used for mild depression
      - Psychotherapy plus medication is recommended for moderate to severe depression
      - Treatment should continue for at least 6 mo
      - Ongoing management should include assessment in key domains (school, home, social setting)
  - Reassessment and referral recommended if no improvement after 6-8 wsks of treatment
  - For adolescents with moderate/severe depression and coexisting psychosis and/or substance abuse, consider referral

Dementia Quick Screen

- 3 simple tests, takes about 2 min
- Use when suspect mild cognitive impairment or when patient is at high risk
- Screen involves:
  1. 3 word recall (normal = recalls 2-3 words)
  2. Naming animals in 1 min (normal = > 12 in one min)
  3. Clock Drawing – including numbers and hands so time shows 10 min past 11 (normal = correct number/hand placing, or only minor spacing problems)
- Interpretation: If all 3 results within normal range, cognitive impairment unlikely.
- If any results abnormal, possible cognitive impairment, further evaluation necessary.

Must Ask About/Rule Out

- Suicidal/homicidal ideation
- Psychosis
- Substance use/abuse/withdrawal
- Anxiety
- Bipolar/manic/hypomanic episodes
- Bereavement
- Intimate partner violence
- Post-partum depression
- Organic cause

Differential Diagnosis

- Other psychiatric disorders (e.g., anxiety, personality, bipolar, adjustment disorder, schizophrenia, seasonal affective disorder, substance abuse/withdrawal)
- Cancer (50% of patients with tumors, especially of brain, lung, and pancreas, develop symptoms of depression before the diagnosis of cancer is made)
- Chronic fatigue syndrome
- Early dementia
- Endocrine (e.g., hyper/hypothyroidism, DM, adrenal disorders)
- Infections (mononucleosis)
- Liver failure, renal failure
- Medication side effects (β-blockers, benzodiazepines, glucocorticoids, interferon)
- Menopause
- Neurological (Parkinson’s, MS)
- Vitamin deficiency (pemphigus, pellagra)
Diabetes Mellitus

- see Endocrinology: E6

Epidemiology
- incidence of type 2 DM is rising dramatically as a result of an aging population, rising rates of obesity, and sedentary lifestyles
- leading cause of new-onset blindness and renal dysfunction
- adults with DM are twice as likely to die prematurely, compared to persons without DM

Risk Factors
- type 1 DM
  - personal or family history of autoimmune disease
- type 2 DM
  - first degree relative with DM
  - age ≥40
  - obesity (especially abdominal), HTN, hyperlipidemia, CAD, vascular disease
  - prior GDM, macrosomia baby (>8 lb 13 oz)
  - PCOS
  - history of IGT or IFG
  - presence of complications associated with DM
  - presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  - medications: glucocorticoids, atypical antipsychotics, HAART
- both
  - member of a high risk population (e.g. Aboriginal, Hispanic, Asian, or African descent)

Diagnosis
- persistent hyperglycemia is the hallmark of all forms of DM

Table 12. Common Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Action</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>paroxetine (Paxil®)</td>
<td>Block serotonin reuptake</td>
<td>Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase QT interval (baseline ECG is suggested)</td>
<td>First-line therapy for youth is fluoxetine; paroxetine is not recommended for youth (controversial)</td>
</tr>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor®)</td>
<td>Block serotonin and NE reuptake</td>
<td>Insomnia, tremors, tachycardia, sweating</td>
<td></td>
</tr>
<tr>
<td>SDRI</td>
<td>bupropion (Wellbutrin®)</td>
<td>Block dopamine and NE reuptake</td>
<td>Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs</td>
<td>Often chosen for lack of sexual side effects, can be used for augmentation of anti-depressant effects with other classes of medication</td>
</tr>
<tr>
<td>TCA</td>
<td>amitriptyline (Elavil®)</td>
<td>Block serotonin and NE reuptake</td>
<td>Sexual dysfunction, weight gain, tremors, tachycardia, sweating</td>
<td>Narrow therapeutic window, lethal in overdose</td>
</tr>
</tbody>
</table>

Prognosis
- up to 40% resolve spontaneously within 6-12 mo
- risks of recurrence: 50% after 1 episode; 70% after 2 episodes; 90% after 3 episodes
Table 13. Diagnosis of Prediabetes and Diabetes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>One of the following on 2 occasions:</td>
</tr>
<tr>
<td></td>
<td>- Random BG ≥200 mg/dL OR</td>
</tr>
<tr>
<td></td>
<td>- Fasting BG ≥126 mg/dL OR</td>
</tr>
<tr>
<td></td>
<td>- BG 2 h post 75 g OGTT ≥200 mg/dL OR HbA1c ≥6.5% (in adults)</td>
</tr>
<tr>
<td></td>
<td><strong>If asymptomatic (and meet any of the above criteria) a repeat test must be done to</strong></td>
</tr>
<tr>
<td></td>
<td><strong>confirm the diagnosis. If symptomatic (fatigue, polyuria, polydipsia, unexplained weight</strong></td>
</tr>
<tr>
<td></td>
<td><strong>loss), the diagnosis is made with one test.</strong></td>
</tr>
<tr>
<td>Impaired Fasting Glucose (IFG)</td>
<td>Fasting BG = 110-124 mg/dL</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance (IGT)</td>
<td>BG 2 h post 75 g OGTT = 141-198 mg/dL</td>
</tr>
</tbody>
</table>

Screening
- type 2 DM
  - FBG in everyone ≥40 q3yr, or at high risk using the CANRISK calculator
  - more frequent and/or earlier testing if presence of ≥1 risk factor (see above)
- GDM (see Obstetrics, OB14)
  - all pregnant women between 24-28 wk gestation

Goals of Therapy

Table 14. Goals of Therapy in Diabetes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Avoid complications (e.g. ketoacidosis, hyperglycemia, infection)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prevent long-term complications (microvascular and macrovascular)</td>
</tr>
<tr>
<td></td>
<td>Minimize negative sequelae associated with therapies (e.g. hypoglycemia, weight gain)</td>
</tr>
</tbody>
</table>

Fasting or Preprandial BG
- Ideal: 72-126 mg/dL
- Suboptimal: 128-180 mg/dL; action may be required
- Inadequate: >180 mg/dL; action required

HbA1c
- ≤7% or ≤6.5% in some type 2 DM patients at risk for nephropathy
- Suboptimal: 7-8.4%
- Inadequate: >8.4%

2 h Postprandial BG
- 90-180 mg/dL if HbA1c target met
- 90-144 mg/dL if HbA1c target not met

Blood Pressure
- <130/80 in adults (DM and HTN guidelines)

Lipids
- LDL <36 mg/dL
- Triglycerides <27 mg/dL
- Total cholesterol/HDL ratio <72 mg/dL

Assessment and Monitoring

Table 15. Assessment and Monitoring

<table>
<thead>
<tr>
<th>Initial Assessment</th>
<th>q2-4mo</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms of hyperglycemia, ketoacidosis, hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional inquiry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sexual function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Physical Exam |        |         |
| General: Ht, Wt, BMI, BP, WC |        |         |
| Head and neck: fundoscopy, thyroid exam |        |         |
| Cardiovascular exam: signs of PVD, pulses, bruits |        |         |
| Abdominal exam (e.g. for organomegaly) |        |         |
| Hand/foot/skin exam |        |         |
| Neurological exam |        |         |

- DM-directed history
- Screen for awareness and frequency of hyperglycemia and DKA
- Glucose monitoring
- Use of insulin and oral agents
- Sexual function
- Lifestyle counseling
- Psychosocial issues
- Complete neurological exam for peripheral neuropathy
- Remainder of exam as per PHE

- DM-directed history
- Screen for awareness and frequency of hyperglycemia and DKA
- Glucose monitoring
- Use of insulin and oral agents
- Sexual function
- Lifestyle counseling
- Psychosocial issues
- Complete neurological exam for peripheral neuropathy
- Remainder of exam as per PHE

Dietary Advice for Treatment of Type 2 DM in Adults
- Cochrane DB Syst Rev 2009;2:CDO005270
- A meta-analysis, using 18 studies comprising 5,168 patients, investigated the effectiveness of diet control, physical activity, behavioral weight programs, and weight control interventions in adults with pre-DM. The analysis was limited by heterogeneous patient populations, but when compared with usual care, weight loss was 2.8 kg and BMI decrease was 1.3 kg/m² at 1 yr. Modest but non-significant improvements in glycemic control, BP and blood lipid concentrations were noted. Studies with a follow-up of 3-6 yr showed a significant decrease in DM onset when compared with controls.

Dietary Advice for Treatment of Type 2 DM in Adults
- Cochrane DB Syst Rev 2007;3:CDO04097
- A meta-analysis, using 36 articles reporting a total of 18 trials following 7,481 participants, showed that there is no high quality data on the efficacy of dietary treatment of type 2 DM. After 6 and 12 mo, adoption of exercise improved HbA1c.
Table 15. Assessment and Monitoring (continued)

<table>
<thead>
<tr>
<th>Initial Assessment</th>
<th>q2-4mo</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FBG, HbA1c, fasting lipids, Cr, microalbumin:creatinine ratio</td>
<td>• HbA1c q3mo</td>
<td>• Fasting lipid profile</td>
</tr>
<tr>
<td>• ECG</td>
<td>• FBG as needed</td>
<td>• Resting or exercise ECG if age &gt;35</td>
</tr>
<tr>
<td>• Lipid profile</td>
<td></td>
<td>• Dipstick analysis for gross proteinuria; if negative: annual microalbuminuria screening with random albumin:creatinine ratio for type 2 DM and type 1 DM (5 yr post puberty)</td>
</tr>
<tr>
<td>• Microalbuminuria</td>
<td></td>
<td>If positive: 24 h urine for endogenous creatinine clearance rate and microalbuminuria q6-12mo</td>
</tr>
</tbody>
</table>

**Management**
- Nutritional and physical education
- Consider referral to DM education program if available
- Monitoring BG: explain methods and frequency
- Medication counseling: oral hypoglycemics and/or insulin, method of administration, dosage adjustments
- Pneumococcal vaccination
- Ophthalmology consult
  - type 1 DM within 5 yr
  - type 2 DM at diagnosis
  - Assess progress towards long-term complications
  - Adjust treatment plan if necessary
  - Calibrate home glucose monitor
  - Arrange ophthalmology follow-up annually for type 1 DM and q2yr for type 2 DM
  - Influenza vaccination annually

**Nonpharmacologic Management**
- **diet**
  - all diabetics should see a registered dietician
  - can reduce HbA1c by 1-2%
  - strive to attain healthy body weight
  - decrease combined saturated fats and trans-fatty acids to <10% of calories
  - avoid simple sugars, encourage complex carbohydrates, choose low glycemic-index foods
- **physical activity and exercise**
  - at least 150 min of aerobic exercise per wk, plus 2 sessions per wk of resistance exercise is recommended
  - encourage 30-45 min of moderate exercise 4-7 d/wk
  - promote cardiovascular fitness: increases insulin sensitivity, lowers BP, and improves lipid profile
  - if insulin treated, may require alterations of diet, insulin regimen, injection sites, and self-monitoring

**Self-Monitoring of Blood Glucose**
- type 1 DM: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
- type 2 DM: recommendations vary based on treatment regimen (e.g., insulin dependent requires more frequent monitoring - refer to 2014 American Practice Guidelines)
- if FBG >252 mg/dL, perform ketone testing to rule out DKA
- if bedtime level is <126 mg/dL, have bedtime snack to reduce risk of nocturnal hypoglycemia

![Figure 4. Types of insulin preparation](image-url)
Figure 5. Management of hyperglycemia in type 2 diabetes

**Hypoglycemic Agents (Type 2 DM)**
- oral
  - biguanide: metformin (Glucophage™)
  - thiazolidinedione: troglitazone (Rezulin™), rosiglitazone (Avandia™), pioglitazone (Actos™)
  - α-glucosidase inhibitor: acarbose (Precose™)
  - nonsulfonylureas: nateglinide (Starlix™), repaglinide (GlucoNorm™)
  - sulfonylureas: glyburide (DiaBeta™), glimepiride (Amaryl™), gliclazide (Diamicon™)
  - DPP-4 inhibitor: sitagliptin (Januvia™)
- injectable
  - GLP-1 analogue: liraglutide (Victoza™)

**Other Medications Used in DM**
- ACEI for
  - all hypertensive diabetics
  - elevated microalbuminuria (30-300 mg albumin in urine in 24 h)
  - overt nephropathy (>300 mg albumin in urine in 24 h)
- ARBs are second line for these conditions
• ASA 81 mg OD for secondary prevention of CVD (should not be used for primary prevention of CVD in people with DM)
• statins
  ▪ as required to attain target lipid profile (LDL-C <36 mg/dL)

## Diarrhea

• see Gastroenterology, G15, and Infectious Diseases, ID11

### Definition

• passage of 3 or more loose or liquid stools in a day or more frequently than is normal for the individual (WHO definition)
• can be acute (<14 d duration) or chronic (>14 d duration)

### Etiology and Clinical Features

- acute diarrhea
  ▪ majority of cases are self-limiting
  ▪ most commonly caused by viral infection (e.g. rotavirus, norovirus)
  ▪ fever and bloody stools increase probability of bacterial infection
  ▪ consider *C. difficile* infection if recent hospitalization, recent antibiotic use (e.g. broad spectrum antibiotics, fluoroquinolones, clindamycin), chronic use of PPIs, age >65, immunosuppression

- chronic diarrhea
  ▪ most commonly of non-infectious etiology
  ▪ common causes include drugs (e.g. laxatives, antibiotics), infection (e.g. bacteria, parasites), inflammation (e.g. IBD, diverticulitis), neoplasia (e.g. colon cancer), malabsorption (e.g. celiac disease), maldigestion (e.g. lactose intolerance), and idiopathic

### Treatment

- acute diarrhea: ensure adequate hydration, treat underlying cause (e.g. antibiotics for bacterial infection)
- chronic diarrhea: nonspecific treatment often required before workup is complete
  ▪ oral rehydration solution (if needed): offset electrolyte imbalances
  ▪ lifestyle modification (dietary changes, exercise)
  ▪ fiber (e.g. psyllium): commonly used as adjunctive treatment
  ▪ antidiarrheal opiates (e.g. loperamide): most effective nonspecific treatment
  ▪ should be used on a scheduled basis before meals rather than prn

## Dizziness

• see Otolaryngology, OT6

### Epidemiology

• 70% see general practitioners initially; 4% referred to specialists
• frequency proportional to age; commonest complaint of ambulatory patients age >75
Differential Diagnosis

**Vertigo (vestibular)**
- Objective (external world seems to revolve around individual) or subjective (individual revolves in space)

- **Central (15%)**
  - Brainstem
  - Cerebellar

- **Peripheral (85%)**
  - Inner ear
  - Vestibular nerve

- Psychogenic Diagnosis of exclusion

- **Vascular**
  - BPPV
  - Basilar migraine
  - TIAs
  - Orthostatic hypotension
  - Stokes-Adams syndrome
  - Anhydrotic
  - CHF

- **Ocular**
  - Decreased visual acuity

**Nonvertiginous (nonvestibular)**
- Feeling “light-headed,” “giddy,” “blazed,” “mentally confused,” or “disoriented”

- **Central (15%)**
  - Brainstem
  - Cerebellar

- **Peripheral (85%)**
  - Inner ear
  - Vestibular nerve

**History**
- Clarify type of dizziness: vertigo, pre-syncpe, disequilibrium, light-headedness
- Duration (seconds, minutes, hours, days, weeks, or persistent)
- Exacerbations
  - Worse with head movement or eye closure (vestibular)
  - No change with head movement and eye closure (nonvestibular)
  - Worse with exercise (cardiac/pulmonary causes)
- Associated symptoms
  - Neurologic (central)
    - Transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
    - Persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)
  - Audiologic (peripheral)
    - Hearing loss, tinnitus, otalgia, aural fullness
  - Others
    - N/V (peripheral vestibular disorders)
    - SOB, palpitations (hyperventilation, cardiac problem)
- General medical history
  - HTN, DM, heart disease, fainting spells, cerebrovascular disease, migraines
  - Otoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - Hypotension (secondary to diuresis): furosemide, caffeine, alcohol

**Physical Exam/Investigations**
- Syncope
  - Cardiac (orthostatic changes in vials), peripheral vascular, and neurologic exams
  - Blood work, ECG, 24 h Holter, treadmill stress test, loop ECG, tilt table testing, carotid and vertebral doppler, EEG
- Vertiginous
  - ENT and neurologic exams
  - Dix-Hallpike, consider audiometry and MRI if indicated
- Non-syncope, non-vertiginous
  - Cardiac and neurologic exams
  - 3-min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG

**Treatment**
- Guided by history, physical exam, and investigations
- Include education, lifestyle modification, physical maneuvers (e.g. Epley for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy, and surgery
- Refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or atypical presentation

---

**DDx of Vertigo**

- **BPPV =** benign paroxysmal positional vertigo
- **TIA =** transient ischemic attack
- **VBI =** vertebral basilar insufficiency

**DDx of Vertigo**

- **Onset** sudden, sudden, gradual, insidious
- **Duration** seconds, days, minutes, hours, chronic
- **Hearing**
  - Loss
  - **Tinnitus**
  - **Neuro Sx**

**Figure 6. Differential diagnosis of dizziness**

**Dix-Hallpike Test**
- Have the patient seated with legs extended and head at 45° rotation
- Rapidly shift patient to supine position with head fully supported in slight extension (for 45 s)
- Observe for rotatory nystagmus and ask about sensation of vertigo

**Vertigo**
- Objective (external world seems to revolve around individual) or subjective (individual revolves in space)

**Nonvertiginous**
- Feeling “light-headed,” “giddy,” “blazed,” “mentally confused,” or “disoriented”

**Etiology**

- Central (15%)
  - Brainstem
  - Cerebellar

- Peripheral (85%)
  - Inner ear
  - Vestibular nerve

- Psychogenic Diagnosis of exclusion

- Vascular
  - BPPV
  - Basilar migraine
  - TIAs
  - Orthostatic hypotension
  - Stokes-Adams syndrome
  - Anhydrotic
  - CHF

- Ocular
  - Decreased visual acuity
Domestic Violence/Elder Abuse

INTIMATE PARTNER VIOLENCE

Definition
- includes physical, sexual, emotional, psychological, and financial abuse
  (see Emergency Medicine, ER29)

Epidemiology
- lifetime prevalence of intimate partner violence against women is between 25-30%
- women who experience abuse have increased rates of injury, death, and health consequences including 50-70% increase in gynecological, central nervous system, stress-related problems
- occurs in all socioeconomic, educational, and cultural groups with increased incidence in pregnancy, disabled women, and 18-24 age group
- 25-50% chance of child abuse or neglect in families where partner abuse occurs
- physician recognition rates as low as 5%

Presentation
- multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
- may also present with injuries inconsistent with history

Management
- screen ALL patients
  - always have a high index of suspicion
  - asking about abuse is the strongest predictor of disclosure
  - several screening tools (see sidebar) exist to identify victims of partner violence
  - make sure to determine the victim's level of immediate and long-term danger and ask if there are weapons in the house
- ensure patient safety
  - victim most at risk for homicide when attempting to leave home or following separation
  - provide community resources
  - safety planning includes ensuring that there is access to an exit in the home, establishing a safe place to go and having money, clothes, keys, medications, important documents, and other emergency items prepared should the patient need to leave quickly
  - shelter or helpline number with legal advocacy and counseling services
  - involve social workers or domestic violence advocates
- appointment for follow-up to assess whether condition is better or worse
- reassure patient she/he is not to blame and that the assault is a crime
  - goal is to convey the message that "As your doctor, I am concerned for your safety" and "Your partner has a problem that he/she needs help with" and "I want to help you"
  - reporting suspected or known child abuse is mandatory (see Emergency Medicine, ER59)
- DOCUMENT all evidence of abuse-related visits for medico-legal purposes

ELDER ABUSE

- see Geriatric Medicine, GM4

Dyspepsia

- see Gastroenterology, G10

Definition and Clinical Features
- defined as epigastric pain or discomfort
- can be associated with fullness, belching, bloating, heartburn, food intolerance, N/V

Epidemiology
- annual incidence 1-2%, prevalence 20-40%

Etiology
- common: functional, PUD, GERD, gastritis
- others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

History
- symptoms may not be useful in finding cause
- association with food, anorexia, N/V alcohol, NSAID use
Investigations and Management
- lifestyle modifications: dietary changes, smaller and more frequent meals, avoid supine position right after meals, decreased EtOH consumption, smoking cessation
- empiric therapy: H₂ receptor blockers, PPIs for short periods of time (8 wk with taper)
- testing for H. pylori: serology, urea breath test
- upper endoscopy (preferred), upper GI series

Dyspnea
- see Respiratory, R3 and Emergency Medicine, ER27

History and Physical Exam
- history
  - cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema
  - asthma, allergy, eczema, ASA/NSAID sensitivity, nasal polyps
  - constitutional symptoms
  - smoking, recreational drugs, medications
  - occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  - travel and birth place
  - FHx of atopy
- physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

Investigations
- CXR, ECG
- PFTs, ABG acutely if indicated

Management
- ABCs: send to ED if in severe respiratory distress
- depends on cause

Dysuria
- see Urology, U10

Definition
- the sensation of pain, burning, or discomfort on urination

Epidemiology
- in adulthood, more common in women than men
- approximately 25% of women report one episode of acute dysuria per yr
- most common in women age 25-54 and in those who are sexually active
- in men, dysuria becomes more prevalent with increasing age

Etiology
- infectious
  - most common cause
    - presents as cystitis, urethritis, pyelonephritis, vaginitis, cervicitis, epididymo-orchitis, or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, radiation, drugs/chemicals, foreign bodies, trauma, neoplasm, kidney stones, inflammatory diseases, endometriosis, psychogenic

Table 16. Etiology, Signs and Symptoms of Common Causes of Dysuria

<table>
<thead>
<tr>
<th>Infection</th>
<th>Etiology</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI/Cystitis</td>
<td>KEEPS bacteria (Klebsiella, E. coli, Enterobacter, Proteus mirabilis, Pseudomonas, S. saprophyticus)</td>
<td>Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)</td>
</tr>
<tr>
<td>Urethritis</td>
<td>C. trachomatis, N. gonorrhoeae, Trichomonas, Candida, herpes</td>
<td>Initial dysuria, urethral/vaginal discharge, history of STD</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>Candida, Gardnerella, Trichomonas, C. trachomatis, atrophic, herpes, lichen sclerosis</td>
<td>External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>E. coli, C. trachomatis, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas</td>
<td>Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>E. coli, S. saprophyticus, Proteus mirabilis, Enterobacter, Klebsiella, Pseudomonas</td>
<td>Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, N/V</td>
</tr>
</tbody>
</table>
Investigations
- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteriuria, hematuria
- urine C&S
- CBC and differential if suspecting pyelonephritis
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomomas, endocervical/urethral swab or urine PCR for N. gonorrhoeae and C. trachomatis
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P64 for UTI in children

Management
- see Antimicrobial Quick Reference, FM52 for treatment
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic, due to risk of preterm labor; need to follow with monthly urine cultures and retreat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
- urethritis
  - when swab or PCR is positive for chlamydia or gonorrhea must report to Public Health
  - all patients should return 4-7 d after completion of therapy for clinical evaluation

Epistaxis
- see Otolaryngology, OT27

Erectile Dysfunction
- see Urology, U30

Definition
- consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance of ≥3 mo duration

Epidemiology
- ~20% of men age 40; ~50% of men age 70

Etiology
- organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, DM), anatomic (structural abnormality, e.g. Peyronie’s), neurologic (post-operative, DM), medications (clonidine, antihypertensives, psychotropics)
- psychogenic (10%)

Table 17. Differentiation Between Organic and Psychogenic Erectile Dysfunction

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Organic</th>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Acute</td>
</tr>
<tr>
<td>Circumstances</td>
<td>Global</td>
<td>Situational</td>
</tr>
<tr>
<td>Course</td>
<td>Constant</td>
<td>Varying</td>
</tr>
<tr>
<td>Non-Coital Erection</td>
<td>Poor</td>
<td>Rigid</td>
</tr>
<tr>
<td>Morning Erection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Psychosexual Problem</td>
<td>Secondary</td>
<td>Long history</td>
</tr>
<tr>
<td>Partner Problem</td>
<td>Secondary</td>
<td>At onset</td>
</tr>
<tr>
<td>Anxiety and Fear</td>
<td>Secondary</td>
<td>Primary</td>
</tr>
</tbody>
</table>

Walsh: Campbell’s Urology, 8th ed. Table 46-4
History

- comprehensive sexual, medical, and psychosocial history
- time course
  - last satisfactory erection
  - gradual or sudden onset
  - attempts at sexual activity
- quantify
  - presence of morning or night time erections
  - stiffness (scale of 1-10)
  - ability to initiate and maintain an erection with sexual stimulation
  - erection stiffness during sex (scale of 1-10)
- qualify
  - partner or situation specific
  - loss of erection before penetration or climax
  - degree of concentration required to maintain an erection
  - percentage of sexual attempts satisfactory to patient and/or his partner
  - significant bends in penis or pain with erection
  - difficulty with specific positions
  - impact on quality of life and relationship

Investigations

- hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
- risk factor evaluation: fasting glucose, HbA1c, lipid profile
- others: TSH, CBC, urinalysis
- specialized testing
  - psychological and/or psychiatric consultation
  - in-depth psychosexual and relationship evaluation
  - nocturnal penile tumescence and rigidity (NPTR) assessment
  - vascular diagnostics (e.g. doppler studies, angiography)

Management

Table 18. Management of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
<th>Pharmacologic</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes (alcohol, smoking, exercise)</td>
<td>Oral agents</td>
<td>Implants</td>
</tr>
<tr>
<td>Relationship/sexual counseling</td>
<td>Suppository</td>
<td>Vascular repair</td>
</tr>
<tr>
<td>Vacuum devices</td>
<td>Male urethral suppository for erection (MUSE)</td>
<td>Realignment</td>
</tr>
</tbody>
</table>

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors
  - α- adrenergic blockers (e.g. yohimbine)
  - serotonin antagonist and reuptake inhibitor (e.g. trazodone)
  - testosterone – currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications)

Table 19. Phosphodiesterase Type 5 Inhibitors

<table>
<thead>
<tr>
<th>Examples</th>
<th>Dosing (1 dose/d)</th>
<th>Specifics</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil (Viagra®)</td>
<td>25-100 mg/dose</td>
<td>Take 0.5-4 h prior to intercourse May last 24 h</td>
<td>Flushing, headache, indigestion</td>
<td>Not to be used in patients taking nitrates</td>
</tr>
<tr>
<td>tadalafil (Cialis®)</td>
<td>5-20 mg/dose</td>
<td>Effects may last 36 h</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>vardenafil (Levitra®)</td>
<td>2.5-20 mg/dose</td>
<td>Take 1 h prior to intercourse</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>

Fatigue

Epidemiology

- 25% of office visits to family physicians
  - peaks in ages 20–40
  - F:M = 3-4:1
- 50% have associated psychological complaints/problems, especially if <6 mo duration
Differential Diagnosis

Table 20. Differential Diagnosis of Fatigue: PS VINDICATE

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong> Psychogenic</td>
<td>Depression, life stresses, anxiety disorder, chronic fatigue syndrome, fibromyalgia</td>
</tr>
<tr>
<td>Physiologic</td>
<td>Pregnancy, excessive caregiving demands (young children, elderly)</td>
</tr>
<tr>
<td>S Sleep disturbance</td>
<td>Obstructive sleep apnea, sleep disorder, poor sleep hygiene, BPH, shift work, pain</td>
</tr>
<tr>
<td>Sedentary</td>
<td>Unhealthy/sedentary lifestyle</td>
</tr>
<tr>
<td>V Vascular</td>
<td>Stroke</td>
</tr>
<tr>
<td>I Infectious</td>
<td>Viral (e.g. mononucleosis, hepatitis, HIV), bacterial (e.g. TB), fungal, parasitic</td>
</tr>
<tr>
<td>N Neoplastic</td>
<td>Any malignancy, lymphoma, multiple myeloma, breast cancer</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Anemia (Fe2+ deficiency, B12 deficiency)</td>
</tr>
<tr>
<td>Neuropenic</td>
<td>Myasthenia gravis, multiple sclerosis, Parkinson’s disease</td>
</tr>
<tr>
<td>D Drugs</td>
<td>B-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics, antidepressants</td>
</tr>
<tr>
<td>I Idiopathic</td>
<td></td>
</tr>
<tr>
<td>C Chronic illnesses</td>
<td>CHF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease</td>
</tr>
<tr>
<td>A Autoimmune</td>
<td>SLE, RA, mixed connective tissue disease, polymyalgia rheumatica</td>
</tr>
<tr>
<td>T Toxin</td>
<td>Substance abuse (e.g. alcohol), heavy metal</td>
</tr>
<tr>
<td>E Endocrine</td>
<td>Hypothyroidism, DM, Cushing’s syndrome, adrenal insufficiency, pregnancy</td>
</tr>
</tbody>
</table>

Common causes are in **bold**

Investigations

- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical exam
- investigations should be guided by history and physical exam and may include
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vit B12, serum protein electrophoresis, Bence-Jones protein, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - urinalysis, CXR, ECG
  - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests

Treatment

- treat underlying cause
- if etiology cannot be identified (1/3 of patients)
  - reassurance and follow-up, especially with fatigue of psychogenic etiology
  - quick follow-up for reassurance
  - supportive counseling, behavioral, or group therapy
  - encourage patient to stay physically active to maximize function
  - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
  - prognosis: after 1 yr, 40% are no longer fatigued

**CHRONIC FATIGUE SYNDROME**

**Definition (CDC 2006)** – must meet both criteria
1. new or definite onset of unexplained, clinically evaluated, persistent or relapsing chronic fatigue, not relieved by rest, which results in occupational, educational, social, or personal dysfunction
2. concurrent presence of at least 4 of the following symptoms for a minimum of 6 mo
   - impairment of short-term memory or concentration, severe enough to cause significant decline in function
   - sore throat
   - tender cervical or axillary lymph nodes
   - muscle pain
   - multi-joint pain with no swelling or redness
   - new headache
   - unrefreshing sleep
   - post-exertion malaise lasting >24 h
- exclusion criteria: medical conditions that may explain the fatigue, certain psychiatric disorders (depression with psychotic or melancholic features, schizophrenia, eating disorders), substance abuse, severe obesity (BMI >45)

**Exercise Therapy for Chronic Fatigue**

*Cochrane Depression, Anxiety, and Neurosis Group*

*Cochrane DB Syst Rev 2004; Issue 3*

**Purpose:** To determine the effectiveness of exercise therapy for Chronic Fatigue Syndrome (CFS).

**Methods:** Systematic review of 5 RCTs with 336 patients of all ages with a clinical diagnosis of CFS.

**Results:** At 12 wk, patients undergoing exercise therapy were less fatigued than controls (SMD -0.77; 95% CI -1.26 to -0.28). Physical functioning was also significantly improved, but there were more dropouts with exercise therapy. Compared with fluoxetine, patients receiving exercise therapy were less fatigued (WMD -1.24; 95% CI -5.31-2.83). Patients receiving combination therapy with exercise therapy and either fluoxetine or patient education, did better than those on monotherapy.

**Conclusions:** Patients may benefit from exercise therapy. Combination therapy with either fluoxetine or education may offer additional benefit. Further high quality trials are needed.
Epidemiology
- F>>M, Caucasians > other groups, majority in their 30s
- found in <5% of patients presenting with fatigue

Etiology
- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency

Investigations
- no specific diagnostic laboratory tests

Treatment
- promote sleep hygiene
- provide support and reassurance that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy (e.g. CBT), family therapy, support groups
- pharmacological
  - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials, antiallergy therapy, antihypotensive therapy

Fever
- see Pediatrics, P54, for fever in pediatric population

Definition
- temperature >100.4°F (38 °C)
- fever in children under 2 must be a rectal temperature for accuracy
- TM not accurate for measurement until child is over the age of 5

Table 21. Differential Diagnosis of Fever

<table>
<thead>
<tr>
<th>Infection</th>
<th>Cancer</th>
<th>Medications</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Leukemia</td>
<td>Allopurinol</td>
<td>Irritable Bowel Syndrome</td>
</tr>
<tr>
<td>Viral</td>
<td>Lymphoma</td>
<td>Captopril</td>
<td>Collagen Vascular Disease</td>
</tr>
<tr>
<td>TB</td>
<td>Other Malignancies</td>
<td>Cimetidine</td>
<td>DVT</td>
</tr>
<tr>
<td></td>
<td>Heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>INH</td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Meperidine</td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barbiturates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
</tbody>
</table>

History
- fever
  - peak temperature, thermometer, route, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
- symptoms of possible source
  - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
  - pneumonia: cough, pleuritic chest pain
  - URTI: cough, coryza, ear pain
  - meningitis: headache, confusion, stiff neck, rash
  - osteomyelitis: bone pain
  - skin: purulent discharge
  - PID: discharge, dyspareunia, lower abdominal pain
  - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
  - medications
  - PE/DVT: swollen legs, pain in calf, SOB, pleuritic chest pain
  - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, day care, contact with TB, foodborne, animals

Possible Investigations
- CBC and differential, blood culture, urine culture, urinalysis
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- LP
Management
• increase fluid intake
• general: sponge bath, light clothing
• acetaminophen/ibuprofen as needed
• treat underlying cause

Headache

• see Neurology, N43

Primary Headaches

Table 22. Primary Headaches

<table>
<thead>
<tr>
<th>Migraine</th>
<th>Tension-Type</th>
<th>Cluster</th>
<th>Caffeine Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>12% of adults, F&gt;M 20% with aura 80% without aura</td>
<td>38% of adults, can be episodic or chronic</td>
<td>&lt;0.1% of adults, M&gt;&gt;F</td>
</tr>
<tr>
<td>Duration</td>
<td>5-72 h</td>
<td>May occur as isolated incident or daily, duration is variable</td>
<td>&lt;3 h at same time of day</td>
</tr>
<tr>
<td>Pain</td>
<td>Classically unilateral and pulsatile, but 40% are bilateral, moderate-severe intensity, N/V, photo-/phonophobia</td>
<td>Mild to moderate pain, bilateral, fronto-occipital or generalized pain, band-like pain, ± contracted neck/ scalp muscles, associated with little disability</td>
<td>Sudden, unilateral, severe, usually centered around eye, frequently awakens patient</td>
</tr>
<tr>
<td>Triggers</td>
<td>Numerous (e.g. food, sleep disturbance, stress, hormonal, fatigue, weather, high altitude) Aggravated by physical activity</td>
<td>Stressful events, NOT aggravated by physical activity</td>
<td>Often alcohol</td>
</tr>
<tr>
<td>Treatment of Acute Headache</td>
<td>1st line: acetaminophen, NSAIDs, ASA ± caffeine 2nd line: NSAIDs 3rd line: 5-HT agonists ± antiemetic</td>
<td>Rest and relaxation NSAIDs or acetaminophen</td>
<td>Sumatriptan Dihydroergotamine High-flow O2 Intranasal lidocaine</td>
</tr>
<tr>
<td>Prophylactic Therapy</td>
<td>1st line: β-blockers 2nd line: TCAs 3rd line: anticonvulsants</td>
<td>Rest and relaxation, physical activity, biofeedback</td>
<td>Lithium carbonate, prednisone, methysergide</td>
</tr>
</tbody>
</table>

Secondary Headaches

• caused by underlying organic disease
• account for <10% of all headaches, may be life-threatening
• etiology
  ▪ aneurysm
  ▪ medication overuse headache
  ▪ space-occupying lesion
  ▪ systemic infection (meningitis, encephalitis)
  ▪ stroke
  ▪ subarachnoid hemorrhage
  ▪ systemic disorders (thyroid disease, HTN, pheochromocytoma, etc.)
  ▪ temporal arteritis
  ▪ traumatic head injuries
  ▪ TMJ or C-spine pathology
  ▪ serious ophthalmological and otolaryngological causes of headache
• treatment
  ▪ based on underlying disorder
  ▪ analgesics may provide symptomatic relief

Investigations

• indicated only when red flags are present and may include:
  ▪ CBC for suspected systemic or intracranial infection
  ▪ ESR for suspected temporal arteritis
  ▪ neuroimaging (CT or MRI) to rule out intracranial pathology
  ▪ CSF analysis for suspected intracranial hemorrhage, infection

Migraine Screen

POUND
P: pulsatile quality
O: over 4-72 h
U: unilateral
N/V: disabling intensity
D: if ≥4 present then a diagnosis is likely (+ LR = 24)

Acupuncture for Migraine Prophylaxis

Cochrane DB Syst Rev 2009;4:CD001218

Study Meta-analysis of 22 RCTs.

Population: 4,419 participants with diagnosed migraine.

Intervention: Preventive treatment with acupuncture, sham acupuncture, no prophylactic treatment/routine care only, other interventions.

Main Outcome Measure: Proportion of responders in 3-4 mo.

Other Outcomes: Frequency of migraine attacks, number of migraine days, headache frequency.

Results: Patients receiving acupuncture had higher response rates and fewer headaches after 3-4 mo than those with no prophylactic treatment or routine care only. There was no statistically significant difference between “true” vs. “sham” acupuncture.

Conclusion: Acupuncture is a viable prophylactic treatment option for migraine attacks. Selecting specific points for acupuncture is not as important as believed by practitioners.
Hearing Impairment

- see Otolaryngology: OT9

Definition
- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

Epidemiology
- prevalence increases with age (6% of 35-44 yr old, 43% of 65-84 yr old)
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people over 65
- associated with significant physical, functional, and mental health consequences

Classification
- conductive (external sound does not reach the middle ear)
- sensorineural involving the inner ear, cochlea, or auditory nerve
- mixed

Assessment
- infants
  - universal newborn hearing screening program
- elderly
  - presbycusis is characterized by the progressive, symmetric loss of high-frequency hearing
  - tinnitus, vertigo, and disequilibrium may be present
  - can cause low self-esteem, isolation, and depression
- whispered-voice test
  - whisper 6 test words 6 in to 2 ft away from the patient’s ear out of the visual field, ask patient to repeat the words (with non-test ear distraction)
- tuning fork test (to distinguish conductive from sensorineural hearing loss)
  - Rinne and Weber (not for general screening)
- formal audiologic assessment
  - pure tone, air, and bone conduction testing
  - speech audiometry
  - impedance audiometry

Management
- counsel about noise control and hearing protection programs (Grade A evidence)
- investigations in patients with unexplained sensorineural hearing loss
  - blood sugar, CBC+ differential, TSH, syphilis testing
- referral
  - refer patients with hearing loss for a complete audiological examination
  - unclear etiology of hearing loss: referral to ENT
  - sudden hearing loss: urgent referral as treatment success is related to early treatment
- patients with progressive asymmetric sensorineural hearing loss should have an MRI/CT scan to exclude vestibular schwannoma (acoustic neuroma)
- hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can dramatically improve quality of life

Hypertension

Hypertension Guidelines are reviewed and updated annually.
For up to date recommendations, please see www.hypertension.ca/chept

Epidemiology
- about 1 in 3 U.S. adults (67 million people) have HTN, only half of these individuals are able to control their condition
- 3rd leading risk factor associated with death

Definition
- HTN
  - BP ≥140/90 mmHg, unless DM (≥130/80 mmHg), or age ≥80 yr (≥150/90 mmHg)
- isolated systolic HTN
  - sBP ≥140 and dBP <90
  - associated with progressive reduction in vascular compliance
  - usually begins in 5th decade
• hypertensive urgency
  ▪ sBP >210 or dBP >120 with minimal or no target-organ damage
• hypertensive emergency
  ▪ severe HTN + acute target-organ damage
  ▪ accelerated HTN
    • significant recent increase in BP over previous hypertensive levels associated with evidence of vascular damage on fundoscopy, but without papilledema
  ▪ malignant HTN
    • sufficient elevation in BP to cause papilledema and other manifestations of vascular damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)

Etiology
• essential (primary) HTN (>90%)
  ▪ undetermined cause
• secondary HTN (10%)
• watch for labile, “white coat” HTN (office-induced elevated BP)

Predisposing Factors
• family history
• obesity (especially abdominal)
• alcohol consumption
• stress
• sedentary lifestyle
• smoking
  ▪ male
  ▪ age >30
  ▪ excessive salt intake/fatty diet
  ▪ African American ancestry
  ▪ dyslipidemia

Table 23. Causes of Secondary Hypertension

<table>
<thead>
<tr>
<th>Common Cause</th>
<th>Renovascular HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney</td>
</tr>
<tr>
<td>Endocrine</td>
<td>1º hyperaldosteronism</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism/hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Hypercalcemia of any cause</td>
</tr>
<tr>
<td>Vascular</td>
<td>Coarctation of the aorta</td>
</tr>
<tr>
<td></td>
<td>Renal artery stenosis</td>
</tr>
<tr>
<td>Drug-Induced</td>
<td>Estrogens/OCP</td>
</tr>
<tr>
<td></td>
<td>MAOIs</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td></td>
<td>Steroids</td>
</tr>
<tr>
<td></td>
<td>Lithium</td>
</tr>
<tr>
<td></td>
<td>Amphetamines</td>
</tr>
<tr>
<td></td>
<td>NSAIDs</td>
</tr>
<tr>
<td></td>
<td>Decongestants</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
</tbody>
</table>

Investigations
• for all patients with HTN
  ▪ electrolytes, Cr, fasting glucose and/or HbA1c, lipid profile, 12-lead ECG, urinalysis
  ▪ self-measurement of BP at home is encouraged
• for specific patient subgroups
  ▪ DM or CKD: urinary protein excretion
  ▪ if suspected renovascular HTN: renal ultrasound, captopril renal scan (if GFR >60 mL/min), MRA/CTA (if normal renal function)
  ▪ if suspected endocrine cause: plasma aldosterone, plasma renin
    • measured from morning samples taken from patients in sitting position after resting 15 min
    • discontinue aldosterone antagonists, ARBs, β-blockers, and clonidine prior to testing
  ▪ if suspected pheochromocytoma: 24 h urine for metanephrines and creatinine
  ▪ echocardiography for left ventricular dysfunction assessment if indicated
**Diagnosis**

**The Expedited Assessment and Diagnosis of Patients with Hypertension**

Focus on Validated Technologies for Blood Pressure Assessment

- Elevated Out of the Office BP Measurement
- Elevated Random Office BP Measurement
- Hypertension Visit 1
  - BP measurement, History and Physical Examination
  - Diagnostic tests ordering at visit 1 or 2
- Hypertension Visit 2 within 1 month
  - BP ≥130/80 mmHg OR
  - BP 140-179/90-109 mmHg with target organ damage or diabetes
- Hypertensive Urgency/Emergency
  - dBP ≥120 mmHg or signs of end organ damage
- Diagnosis of HTN

- BP 140-179/90-109 mmHg
- ABPM (if available)
  - Awake BP ≥135/85 mmHg or
  - 24 hour ≥130/80
  - OR
  - Home BPM (if available)
  - <135/85
- Hypertension Visit 3
  - ≥160 sBP or
  - ≥100 dBP
  - Diagnosis of HTN
  - <160/100 OR
  - ABPM or Home BPM if available
  - ≥140 sBP or
  - ≥90 dBP
  - Diagnosis of HTN
  - <130/90
  - Continue to follow-up
  - Continue to follow-up
  - Diagnosis of HTN

- Hypertension Visits 4-5
- ≥140 sBP or
  - ≥90 dBP
- Diagnosis of HTN
- <130/90
- Repeat Home BPM
  - If <135/85
  - Diagnosis of HTN
  - ≥135 mmHg
  - ≥85 mmHg

- Repeat Home BPM
  - <135/85
  - Diagnosis of HTN

- Hypertension Visit 4
  - ≥160 sBP or
  - ≥100 dBP
  - ABPM or Home BPM if available
  - <160/100

- Hypertension Visit 5
  - ≥140 sBP or
  - ≥90 dBP
  - Continue to follow-up
  - <130/90

**Impact of Health Behavior on Blood Pressure**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and weight control</td>
<td>-6.0</td>
<td>-4.8</td>
</tr>
<tr>
<td>Reduced salt/sodium intake</td>
<td>-5.4</td>
<td>-2.8</td>
</tr>
<tr>
<td>Reduced alcohol intake (heavy drinkers)</td>
<td>-3.4</td>
<td>-3.4</td>
</tr>
<tr>
<td>DASH diet</td>
<td>-11.4</td>
<td>-5.5</td>
</tr>
<tr>
<td>Physical activity</td>
<td>-3.1</td>
<td>-1.8</td>
</tr>
<tr>
<td>Relaxation therapies</td>
<td>-3.7</td>
<td>-3.5</td>
</tr>
<tr>
<td>Multiple interventions</td>
<td>-5.5</td>
<td>-4.5</td>
</tr>
</tbody>
</table>


---

**Figure 7. Assessment of patients with hypertension**

Adapted from: CHEP 2014 Guidelines

**Treatment**

- target BP is <140/90 mmHg, <130/80 mmHg if DM
- lifestyle modification (in all HTN patients)
  - may be sufficient in patients with stage 1 HTN (140-159/90-99)
  - diet
    - follow Dietary Guidelines for Americans (see Nutrition, FM6) and Dietary Approaches to Stop HTN (DASH) (reduced cholesterol and saturated fats)
    - limit daily sodium intake to 65-100 mmol (1.5-2.3 g)
    - potassium/magnesium/calcium supplementations are NOT recommended for HTN
  - moderate intensity dynamic exercise: 30-60 min, 4-7 x/wk; higher intensity exercise is no more effective
  - smoking cessation
  - stress management
  - low-risk alcohol consumption (see Alcohol, FM12)
  - achieve and maintain a healthy BMI (18.5-24.9 kg/m²) and waist circumference (<40.2 in for men, <34.6 in for women); use multidisciplinary approach to weight loss
  - individualized cognitive behavioral interventions for stress management
- pharmacological
  - indications regardless of age (caution with elderly patients)
    - dBP ≥90 mmHg with target organ damage or independent cardiovascular risk factors
    - dBP ≥100 mmHg or sBP ≥160 mmHg without target organ damage or cardiovascular risk factors
    - sBP ≥140 with target organ damage
  - first line antihypertensives: thiazide/thiazide-like diuretic, ACEI (for non-African patients), ARB, long-acting CCB, β-blocker (if age <60)
  - if partial response to standard dose monotherapy, add another first-line drug
  - caution with combination of non-DHP CCB and β-blocker
  - combination of ACEI and ARB is not recommended
  - be cautious of hypokalemia in patients treated with thiazide/thiazide-like diuretic monotherapy
  - if still not controlled or adverse effects, can add other classes of anti-hypertensives
### Table 24. Pharmacologic Treatment of Hypertension in Patients with Unique Conditions

<table>
<thead>
<tr>
<th>Condition or Risk Factor</th>
<th>Recommended Drugs</th>
<th>Alternative Drugs</th>
<th>Not Recommended/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolated Diastolic HTN</strong></td>
<td>Thiazide diuretic, β-blocker, ACEI, ARB, or long-acting CCB (consider ASA and statin in select patients)</td>
<td>Combinations of first-line drugs</td>
<td>β-blocker monotherapy (age &gt;60) or combination of ACEI with an ARB</td>
</tr>
<tr>
<td><strong>Isolated Systolic HTN</strong></td>
<td>Thiazide diuretic, ARB, or long-acting dihydropyridine CCB</td>
<td>Combinations of first-line drugs</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>CAD</strong></td>
<td>ACEI or ARB; β-blocker for patients with stable angina</td>
<td>Long acting CCB, when combination therapy for high risk patients, ACEI/DHP CCB is preferred</td>
<td>Short-acting CCB (nifedipine) or ACEI + ARB is not recommended</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>β-blocker + ACEI (ARB if cannot tolerate ACEI)</td>
<td>Long-acting CCB</td>
<td>ACEI + ARB combination is not recommended</td>
</tr>
<tr>
<td><strong>Left Ventricular Hypertrophy</strong></td>
<td>ACEI, ARB, thiazide, or long-acting CCB</td>
<td>Combination of additional agents</td>
<td>Hydralazine and minoxidil can increase LVH, thus not recommended</td>
</tr>
<tr>
<td><strong>Cerebrovascular Disease (stroke/TIA)</strong></td>
<td>ACEI + diuretic</td>
<td>Combination of additional agents</td>
<td>ACEI + ARB combination after a stroke is not recommended</td>
</tr>
<tr>
<td><strong>Heart Failure</strong></td>
<td>ACEI (ARB if ACEI intolerant) and β-blocker</td>
<td>Spironolactone in patients with NYHA class II-IV</td>
<td>ARB in addition to ACEI Hydralazine/sosorbide dinitrate combination if ARB or ACEI not tolerated/contraindicated</td>
</tr>
<tr>
<td><strong>Dyslipidemias</strong></td>
<td>Does not affect initial treatment recommendations</td>
<td>Combination of additional agents</td>
<td>Thiazide or loop diuretic is recommended as additive therapy. DHP CCB can also be used</td>
</tr>
<tr>
<td><strong>DM with Albuminuria (ACR &gt;2.0 mg/mmol in men and &gt;2.8 mg/mmol in women)</strong></td>
<td>ACEI or ARB (DHCP CCB &gt; HCTZ for combination therapy with ACEI)</td>
<td>Add thiazide diuretic, cardioselective β-blocker, long acting CCB</td>
<td>If serum Cr &gt;150 μmol/L, a loop diuretic should be considered instead of low-dose thiazide diuretic</td>
</tr>
<tr>
<td><strong>DM without Albuminuria (criteria listed above)</strong></td>
<td>ACEI, ARB, DHP CCB, or thiazide diuretic</td>
<td>Combination of first-line drugs or, first-line agents not tolerated, cardioselective β-blocker or non-DHP CCB</td>
<td>Non-DHP CCB not recommended</td>
</tr>
<tr>
<td><strong>Non-Diabetic Chronic Kidney Disease with Proteinuria (urinary protein &gt;500 mg/24 h or ACR &gt;30 mg/mmol)</strong></td>
<td>ACEI (ARB if ACEI intolerant), diuretic as additive therapy</td>
<td>Thiazide for additive anti-hypertensive therapy, loop diuretic for volume overload</td>
<td>ACEI + ARB combination is not recommended</td>
</tr>
<tr>
<td><strong>Renovascular Disease</strong></td>
<td>Same as HTN without other indications</td>
<td>Caution in using ACEI or ARB – monitor for AKI</td>
<td></td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>K+-sparing + thiazide diuretic for patients on salbutamol</td>
<td>β-blocker, unless specific indications like angina or post-MI</td>
<td></td>
</tr>
<tr>
<td><strong>Gout</strong></td>
<td>Thiazide, but asymptomatic hyperuricemia is not a contraindication</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>Low dose thiazide ACEI</td>
<td>β-blocker</td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>Methyldopa Hydralazine</td>
<td>Labetolol</td>
<td>ACEI</td>
</tr>
<tr>
<td><strong>Elderly (&gt;60 yr)</strong></td>
<td>As for uncomplicated isolated diastolic HTN, except for use of β-blocker</td>
<td>β-blocker not recommended as first line treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Emergency</strong></td>
<td>BP &gt;169/90 = labetolol, nifedipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If &gt;3 Cardiovascular Risk Factors or Established Atherosclerotic Disease</strong></td>
<td>Statin (age &gt;40), low-dose ASA (age &gt;50)</td>
<td>Caution with use of ASA in patients with uncontrolled BP</td>
<td></td>
</tr>
</tbody>
</table>


---

**Calcium Channel Blockers**

- Dihydropyridine CCBs
  - amlodipine
  - felodipine
  - nifedipine

- Non-Dihydropyridine CCBs
  - diltiazem
  - verapamil

**How to Combine Antihypertensive Medications (in general)**

- **ACEI**
- β-blocker
- CCB
- Diuretic

**Thiazides as First-Line Antihypertensive Therapy – ALLHAT**

*JAMA 2002;288:2981-2997*

- **Study:** Randomized, double-blind, active-controlled clinical trial with mean follow-up of 4.9 yr.
- **Patients:** 33,357 participants (mean age 47 yr; 53% male, 47% white) with stage 1 or 2 HTN and at least one other CHD risk factor.
- **Intervention:** Participants were randomly assigned to receive chlorthalidone (12.5-25 mg/d), amlodipine (2.5-10 mg/d), or lisinopril (10-40 mg/d). Target BP was <140/90 mmHg, achieved by titrating the assigned study drug, and adding open-label agents when necessary.
- **Outcomes:** The primary outcome was combined fatal CHD or non-fatal MI. Secondary outcomes were all-cause mortality, stroke, combined CHD, and combined CVD.
- **Results:** There were no significant differences in either the primary outcome or all-cause mortality between treatment groups. For amlodipine vs. chlorthalidone, secondary outcomes were similar except for a higher 6 yr rate of heart failure with amlodipine (10.2% vs. 7.7%; p<0.001). For lisinopril vs. chlorthalidone, lisinopril had higher 6 yr rates of combined CVD (33.3% vs. 30.9%; p<0.001), stroke (6.3% vs. 5.6%; p=0.02) and heart failure (6.7% vs. 7.7%; p<0.001).
- **Conclusion:** Thiazide diuretics are superior to CCB and ACEI for preventing one or more major forms of CVD, with similar risks of death and non-fatal MI.
Follow-Up
- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification → q3-6mo
- pharmacological
  - q1-2mo until BP under target for 2 consecutive visits
  - more often for symptomatic HTN, severe HTN, antihypertensive drug intolerance, target organ damage
  - q3-6mo once at target BP
- referral is indicated for cases of refractory HTN, suspected secondary cause or worsening renal failure
- hospitalization is indicated for malignant HTN

Joint Pain

- see Rheumatology, RH3

Table 25. Differential Diagnosis of Joint Pain

<table>
<thead>
<tr>
<th>Localized</th>
<th>Generalized</th>
<th>Inflammatory</th>
<th>Articular</th>
<th>Degenerative</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bursitis</td>
<td>Fibromyalgia</td>
<td>Seropositive</td>
<td></td>
<td>Primary</td>
<td></td>
</tr>
<tr>
<td>Tendonitis</td>
<td>Polymyalgia rheumatica</td>
<td>Systemic lupus erythematosus</td>
<td></td>
<td>Familial Heberden’s node</td>
<td>Neoplastic</td>
</tr>
<tr>
<td>Capsulitis</td>
<td>Myofascial pain syndrome</td>
<td>Scleroderma</td>
<td></td>
<td>Osteoarthritis</td>
<td>Drug-induced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polymyositis/Dermatomyositis</td>
<td></td>
<td>Regional hip or knee</td>
<td>Endocrine (hyperthyroid, hypothyroid, hyperparathyroid)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sjögren’s syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seronegative</td>
<td></td>
<td>Inflammatory bowel disease</td>
<td></td>
<td>Secondary</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriatic arthritis</td>
<td></td>
<td>Metabolic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reactive arthritis</td>
<td></td>
<td>Hemophiliac</td>
<td></td>
</tr>
<tr>
<td>Crystal</td>
<td></td>
<td></td>
<td></td>
<td>Neuropathic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Traumatic</td>
<td></td>
</tr>
<tr>
<td>Infectious/septic</td>
<td></td>
<td>Gout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudogout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydroxyapatite</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-gonococcal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic vasculitis disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

History
- number of joints involved: monoarticular, oligoarticular, polyarticular
- pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
- onset: acute vs. chronic (>6 wk)
- trauma, infection, medications (steroids, diuretics)
- morning stiffness (duration) vs. worse at end of day
- FHx of arthritis
- comorbidities: DM (carpal tunnel syndrome), renal insufficiency (gout), psoriasis (psoriatic arthritis), myeloma (low back pain), osteoporosis (fracture), obesity (OA)
- constitutional symptoms (neoplasm)

Physical Exam
- vitals
- specific joint exams
- systemic features (skin, nails, eyes, hands)

Investigations (Guided by the History and Physical Exam)
- general: CBC and differential, electrolytes, Cr
- acute phase reactants: ESR, CRP, ferritin, albumin, fibrinogen
- complement (C3, C4)
- urinalysis to detect disease complications (proteinuria, active sediment)
- serology (ANA, anti-dsDNA, HLA-B27, anti-Jo-1, anti-Sm, anti-La, anti-Ro, RhF, and anti-CCP, etc.)
- synovial fluid analysis (cell count + differential, culture, Gram stain, microscopy)
- tissue cultures
- radiology (plain film, CT, MRI, U/S, bone densitometry, angiography, bone scan)

Signs and Symptoms of Inflammatory Arthritis

WARM(S) Joints
- Worse with rest, better with activity
- Awakening in the latter half of the night
- Redness around joint
- Morning stiffness (>30 min)
- Soft tissue swelling, erythema

Systemic Features
- Fever (SLE, infection)
- Rash (SLE, psoriatic arthritis)
- Nail abnormalities (psoriatic, reactive arthritis)
- Uveitis (psoriatic, reactive arthritis, ankylosing spondylitis)
- Myalgias (fibromyalgia, myopathy)
- Weakness (polymyositis, neuropathy)
- GI symptoms (scleroderma, IBD)
- GU symptoms (reactive arthritis, gonococccemia)
Treatment

- patient education including lifestyle modifications
- physiotherapy, occupational therapy
- manage pain (acetaminophen, NSAIDs)
- treat specific causes (e.g. antibiotics, DMARDs etc., see Rheumatology, RH30)

Low Back Pain

- see Orthopedics, OR23
- see https://www.bigbackpain.com for more information

Definition

- acute: <6 wk
- subacute: 6-12 wk
- chronic: >12 wk

Epidemiology

- 5th most common reason for visiting a physician
- lifetime prevalence: 90%
- peak prevalence: age 45-60
- most common cause of chronic disability for individuals <45 yr old
- 90% resolve in 6 wk, <5% become chronic

Etiology

- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes
  - pain is worse with movement, better with rest
  - sprain (ligament), strain (muscle), facet joint degeneration, disc degeneration/herniation, spinal stenosis (e.g. spondylosis), spondylolysis, compression fracture, pregnancy
- 2% are non-mechanical causes
  - most concerning when pain is worst at rest and does not change with position
  - surgical emergencies:
    - cauda equina syndrome (areflexia, lower extremity weakness, decreased anal tone, saddle anesthesia, fecal incontinence, urinary retention), AAA (pulsatile abdominal mass)
  - medical conditions
    - neoplastic (primary, metastatic, multiple myeloma)
    - infectious (osteomyelitis, TB)
    - metabolic (osteoporosis, osteomalacia, Paget’s disease)
    - rheumatologic (ankylosing spondylitis, polymyalgia rheumatica)
    - referred pain (perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster)

Physical Exam

- inspection: curvature, posture, gait
- palpation: bony deformities/tenderness, paraspinal muscle bulk/tenderness, trigger points
  - percussion of spine to elicit pain due to fracture or infection
- ROM and peripheral pulses
- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes, sensation)
- special tests
  - straight leg raise (positive if pain at <70 degrees and aggravated by ankle dorsiflexion), positive test is indicative of sciatica
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy

Investigations

- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI

Indications for Lumbar Spine X-Ray

- No improvement after 6 wk
- Fever >100.4°F
- Unexplained weight loss
- Prolonged corticosteroid use
- Significant trauma
- Progressive neurological deficit
- Suspicion of ankylosing spondylitis
- History of cancer (rule out metastases)
- Alcohol/drug abuse (increased risk of osteomyelitis, trauma, fracture)
A Summary of the Guideline for the Evidence-Informed Primary Care Management of Low Back Pain

**Red Flags** help identify rare, but potentially serious conditions. They include:
- Features of Cauda Equina Syndrome including sudden onset of loss of bladder/bowel control, saddle anesthesia (EMERGENCY)
- Severe worsening pain, especially at night or when lying down (URGENT)
- Significant trauma (URGENT)
- Use of steroids or intravenous drugs (URGENT)
- Patient with first episode over 50 years old, especially over 65 (SOON)
- Widespread neurological signs (SOON)

**Yellow Flags** indicate psychosocial barriers to recovery. They include:
- Belief that pain and activity are harmful
- Tension behaviors (Was extended out)
- Low or negative mood, social withdrawal
- Treatment expectations that do not fit best practice
- Problems with claim and compensation
- History of back pain, time-off, other claims
- Problems at work, poor job satisfaction
- Heavy work, unproductive hours (shift work)
- Overprotective family or lack of support

**ACUTE and SUBACUTE** (within 12 weeks of pain onset)

- **1 – 6 WEEKS**
  - Educate patient that low back pain typically resolves within a few weeks (70% in 2 wks, 90% in 6 wks)
  - Prescribe self-care strategies including alternating cold and heat, continuation of usual activities as tolerated
  - Encourage early return to work
  - Recommended physical activity and/or exercise
  - Consider analgesics in this order:
    - Acetaminophen (1st line)
    - NSAIDs (2nd line)
    - Short-acting opioids
  - Spinal traction, TENS not recommended

- **Reassess (including Red Flags) if patient is not returning to normal function or symptoms are worsening**

- **Consider Referral**
  - Physical therapist
  - Chiropractor
  - Osteopathic physician
  - Physician specializing in musculoskeletal medicine
  - Spinal surgeons (for unremitting radicular symptoms)
  - Multidisciplinary pain program (if not returning to work)

**CHRONIC** (more than 12 weeks since pain onset)

- **Prescribe physical or therapeutic exercise**
  - **Analogic Options**
    - Acetaminophen
    - NSAIDs (consider PPI)
    - Low-dose tri cyclic antidepressants
    - Short-term benzodiazepine for flare-ups
  - **Referral Options**
    - Community-based active rehabilitation program
    - Community-based self-management/cognitive behavioral therapy program
  - **Additional Options**
    - Progressive muscle relaxation
    - Acupuncture
    - Massage therapy, TENS as adjunct to active therapy
    - Aqua therapy and yoga

**MODERATE TO SEVERE PAIN**

- **Spinal (for appropriate patients; refer to the Canadian National Spinal Guidelines endorsed by the College of Physicians and Surgeons of Alberta [http://nationalpaincentre.ucalgary.ca/spinal])**
- **Referral Options**
  - Multidisciplinary chronic pain program
  - Epidural steroids (for short-term relief of radicular pain)
  - Prolotherapy, facet joint injections, and surgery in carefully selected patients

**Figure 8. Low back pain treatment**


**Table 26. Approach to Non-Traumatic Low Back Pain**

<table>
<thead>
<tr>
<th>Back Dominant (Pain greatest above gluteal fold)</th>
<th>Leg Dominant (Pain greatest below gluteal fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td><strong>Pattern 3</strong></td>
</tr>
<tr>
<td>Pattern 1 Worse with flexion Constant/intermittent</td>
<td>Pain changes with back movement/position Currently/ previously constant</td>
</tr>
<tr>
<td>Pattern 2 Worse with extension Never worse with flexion Always intermittant</td>
<td>Leg pain can improve but not disappear Positive straight leg raise ± conduction loss Fast responder</td>
</tr>
<tr>
<td><strong>Pattern 4</strong></td>
<td><strong>Pattern 4</strong></td>
</tr>
<tr>
<td>Worse with activity</td>
<td>Improves with rest and posture change Intermediate/short duration</td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td><strong>Sciatica</strong></td>
</tr>
<tr>
<td>Normal neuro exam Fast responder</td>
<td>Neurogenic claudication</td>
</tr>
<tr>
<td>• Improves with extension</td>
<td>Abdominal exercises</td>
</tr>
<tr>
<td>Slow responder No change or worsens with extension</td>
<td>Night lumbar roll</td>
</tr>
<tr>
<td><strong>Likely Pathology</strong></td>
<td><strong>Night lumbar roll</strong></td>
</tr>
<tr>
<td>Arising from intervertebral discs or adjacent ligaments</td>
<td>Medication as required</td>
</tr>
<tr>
<td><strong>Initial Management</strong></td>
<td><strong>Prone extension</strong></td>
</tr>
<tr>
<td>Scheduled extension Lumbar roll Night lumbar roll</td>
<td>Sustained flexion</td>
</tr>
<tr>
<td>Night lumbar roll Medication as required</td>
<td>Pelvic tilt</td>
</tr>
</tbody>
</table>

Menopause/Hormone Replacement Therapy

- see Gynecology, GY31

Epidemiology
- mean age of menopause = 51.4 yr
- a woman will spend over 1/3 of her life in menopause

Clinical Features
- associated with estrogen deprivation
- urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
- blood vessels and heart: vasomotor instability (e.g. hot flashes), increased risk of heart disease
- bones: bone loss, joint/muscle/back pain, fractures, loss of height
- brain: depression, irritability, mood swings, memory loss

Management
- encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1,200-1,500 mg/d) and vitamin D (800-2,000 IU/d)
- hormone replacement therapy (HRT)
  - prescribe for moderate to severe symptoms for no longer than 5 yr; routine use is not recommended
  - regimens: cyclic estrogen-progestin, continuous estrogen-progestin, estrogen only (if no uterus), estrogen patch/gel/cream/ring/vaginal tablet
  - decreases risk of osteoporotic fractures, colorectal cancer
  - increases risk of breast cancer, coronary heart disease, stroke, DVT, and PE
  - initiation of HRT requires a thorough discussion of short- and long-term benefits and risks
- consider venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

Osteoarthritis

- see Rheumatology, RH5

Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, periarticular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (OT/PT), assistive devices (e.g. canes, orthotics, raised toilet seats)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs in the lowest effective dose for the shortest duration of time, along with gastroprotection: COX-2 selective inhibitors (celecoxib/Celebrex, Meloxicam/Mobic®) are recommended if long-term treatment or if high risk for serious GI problems
  - combination analgesics (e.g. acetaminophen and codeine)
  - intra-articular hyaluronic acid injections
  - intra-articular corticosteroid injections (no more than 3-4x/yr) may be helpful in acute flares (benefits last 4-6 wk, can be up to 6 mo)
  - topical NSAID (diclofenac/Pennsaid®)
  - capsaicin cream (Zostrix®)
  - oral glucosamine
  - surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g. debridement, osteotomy, total joint arthroplasty)

Glucosamine Therapy for Treating Osteoarthritis
This meta-analysis of 25 single- and double-blinded randomized controlled trials with 4,963 patients compared glucosamine treatment, administered by any route, against placebo or another treatment.

Conclusions: Glucosamine can decrease pain and functional impairment resulting from OA and is not associated with any side effects compared to placebo. Differences in the effectiveness of Rotta and non-Rotta preparations highlight variability between glucosamine preparations and patients should be made aware of this.
Osteoporosis

- see Endocrinology, E42

- for current guidelines and tools see National Osteoporosis Foundation: http://nof.org/hcp/clinicians-guide

- age-related disease characterized by decreased bone mass and increased susceptibility to fractures

- about 9.9 million Americans are affected by osteoporosis, while an additional 43.1 million have low bone density

- approximately 1 in 2 women and up to 1 in 4 men ≥50 yr will sustain fractures due to osteoporosis

**Management**

- see Endocrinology, E44

**Palliative and End-of-Life Care**

- see Geriatrics, GM12
Rash

- see Dermatology, D5

ATOPIC DERMATITIS
- clinical features
  - affects all ages but is more common in children
  - pruritus is the most common symptom; scratching worsens the rash creating a vicious cycle
- treatment
  - goals: limit itching, repair skin
  - moisturizers, emollients, topical corticosteroids; oral corticosteroids and topical calcineurin inhibitors may be used

SEBORRHEIC DERMATITIS
- clinical features
  - affects all ages but is most common in infants within the first 3 mo of life (e.g. pityriasis capitis or "cradle cap") and adults age 30-60
  - affects the scalp, central face, and anterior chest; often presents as scalp scaling (dandruff) in adolescents and adults
  - may cause mild to marked erythema of the nasolabial fold, often with greasy scaling
- treatment
  - topical antifungals, topical low-potency steroids; topical calcineurin inhibitors may be used

ROSACEA
- clinical features
  - stages: (1) facial flushing, (2) erythema and/or edema and ocular symptoms, (3) papules and pustules, (4) rhinophyma
- treatment
  - topical or oral antibiotics, oral retinoids
  - laser treatment may be an option for progressive telangiectasia or rhinophyma
  - referral may be required to manage rhinophyma, ocular complications, or severe disease

ACNE VULGARIS
- clinical features
  - types: (I) comedonal, (II) papular, (III) pustular, (IV) nodulocystic
  - predilection for the face, neck, upper chest, and back
- treatment
  - mild acne: topical treatments (antibiotics, benzoyl peroxide, retinoids)
  - moderate acne: after topical treatments have failed, add oral antibiotics and consider hormonal therapy
  - severe acne: consider systemic retinoids

ONYCHOMYCOSIS (TINEA UNGUIUM)
- definition: fungal infection of the nail bed, matrix, or plate
- clinical features
  - occurs primarily in adults, most commonly after age 60
  - crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris
  - toenails are affected more often than fingernails
- investigations
  - microscopy of subungual scrapings under KOH preparation, culture
- treatment
  - oral antifungals (terbinafine/Lamisil®, itraconazole/Sporanox®), topical antifungals (ciclopirox/Loprox®)
Sexually Transmitted Diseases

Definition
- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

Epidemiology
- high incidence rates worldwide
- American prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes (increasing incidence of chlamydia and gonorrhea)
  - less common: hepatitis B, HIV, and syphilis (increasing in incidence), trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venerum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

History
- sexual history
  - age of first intercourse, sexual orientation, sexual activity (oral, anal, and/or vaginal intercourse), sexual activity during travel
  - total number of partners in the past yr/mo/wk and duration of involvement with each
- STD history
  - STD awareness, contraception, previous STDs and testing (including Pap tests), partner communication regarding STDs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

Investigations/Screening
- individuals at increased risk, even those who are asymptomatic, should be screened for chlamydia, gonorrhea, hepatitis B, HIV, and syphilis
- Pap test if none performed in the preceding 12 mo

Management
- primary prevention is vastly more effective than treating STDs and their sequelae
- offer hepatitis B vaccine if not immune, offer Gardasil® to women under age 26
- discuss STD risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use condoms or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- an STD patient is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients diagnosed with bacterial STD or trichomonal infection should abstain from sexual activity until treatment completion and for 7 d after treatment for both partners, or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis

When an STD is detected in a prepubertal child, evaluation for sexual abuse is mandatory

STD Risk Factors
-Sexually active males and females < 25 yr old
- Unprotected sex, sexual contact with a known case of STD, previous STD
- New sexual partner or > 2 sexual partners in the past 12 mo
- Street involved, homeless, and/or substance abuse

Sexual History
5 P’s
- Partners (numbers, gender)
- Practices (vaginal, oral, anal insertive/receptive)
- Protection
- Past history of STDs
- Pregnancy prevention

Prophylactic Vaccination Against Human Papillomavirus Infection and Disease in Women: A Systematic Review of Randomized Controlled Trials

CMAJ 2007;177:469-479

Purpose: To evaluate prophylactic HPV vaccination in preventing high- and low-grade cervical lesions, persistent HPV infection, external genital lesions, adverse events, and death using meta-analysis.

Studies: 9 reports from 6 different trials with 40,323 patients were included and all studies were of high methodologic quality. Three studies used the quadrivalent vaccine, two used the bivalent, and one used a monovalent. The longest mean duration of follow-up was 48 mo.

Results: Prophylactic HPV vaccination decreased the frequency of high-grade cervical lesions caused by vaccine-type HPV strains compared to the control group (OR 0.14; 95% CI 0.09-0.21). Vaccinations also prevented persistent HPV infection, low-grade lesions and genital warts, and the reported adverse events were mostly minor. Compared to placebo, there was no difference in serious adverse events or death.

Conclusion: Prophylactic HPV vaccination is highly efficacious in preventing infection and precancerous cervical disease in women aged 15-25 who have not previously been infected with vaccine-type HPV strains.
**Signs and Symptoms**

**Gonococcal Urethritis/Cervicitis (Neisseria gonorrhoeae)**
- M: urethral discharge, unexplained pyuria, dysuria, irritation, testicular swelling, 5x of epididymitis
- F: mucopurulent endocervical discharge, vaginal bleeding, dysuria, pelvic pain, dyspareunia
- M and F: often asymptomatic, can involve rectal symptoms in cases of unprotected anal sex

**Non-Gonococcal Urethritis/Cervicitis (Usually Chlamydia trachomatis)**
- ~70% asymptomatic
- If symptoms appear (usually 2-6 wk after infection) then similar to gonococcal symptoms (see above)

**Human Papillomavirus (genital warts, cervical dysplasia)**
- Most are asymptomatic
- M: cauliflower lesions (condylomata acuminata) on skin/mucosa of penile or anal area
- F: cauliflower lesions and/or pre-neoplastic/neoplastic lesions on cervix/vagina/vulva

**Genital Herpes (HSV-1 and -2)**
- 1° episode: painful vesiculocellular genital lesions ± fever, tender lymphadenopathy, protracted course
- Recurrent episodes: less extensive lesions, shorter course may have “trigger factors”

**Infectious Syphilis (Treponema pallidum)**
- 1°: chancre (painless sore), regional lymphadenopathy
- 2°: rash and flu-like symptoms, meningoitis, H/A, urethritis, retinitis, condyloma lata, mucus lesions, alopecia
- Latent Phase: asymptomatic
- 3°: neurologic, cardiovascular, and tissue complications

**Investigations**

- Specimen collection from 1° and 2° lesions, screen for culture, type-specific serologic testing for HSV-1 vs. HSV-2 antibodies and to determine 1° vs. recurrent episode

**Treatment**

- 1° episode:
  - Acyclovir 200 mg PO 5x/d x 5-10 d or
  - Famciclovir 250 mg PO tid x 5 d or
  - Valacyclovir 1,000 mg PO bid x 10 d

- Recurrent Episode:
  - Acyclovir 200 mg PO 5x/d x 5d or 800 mg PO tid x 2 d or
  - Famciclovir 125 mg PO bid x 5 d or
  - Valacyclovir 500 mg PO bid x 3 d or 1,000 mg PO OD x 3 d

**Complications**

- Chronic neurologic and cardiovascular sequelae, increased risk of acquiring and transmitting HIV

**F = females; M = males**

*NB: if urethritis/cervicitis is suspected, always treat for both gonococcal and non-gonococcal types (i.e. ceftriaxone AND azithromycin)*

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**Sinusitis**

- see Otolaryngology, OT25

**Etiology**

- viral etiology is more common
- viral: rhinovirus, influenza, parainfluenza
- bacterial: S. pneumoniae, H. influenzae, M. catarrhalis

**Management of Acute Sinusitis**

- may provide symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical or oral decongestants
- do not prescribe antihistamines
- intra-nasal corticosteroids if diagnosed with mild to moderate acute bacterial sinusitis
- antibiotics and intra-nasal corticosteroids if diagnosed with severe acute bacterial sinusitis
- ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, >4 episodes/yr, development of complications (e.g. mucocele, orbital extension, meningitis, intra-cranial abscess, venous sinus thrombosis)
Sleep Disorders

- see Respirology, R31 and Neurology, N45

Definition
- most often characterized by one of three complaints:
  - insomnia
    - difficulty falling asleep, difficulty maintaining sleep, early-morning wakening, non-refreshing sleep
  - parasomnias
    - night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behavior during sleep with eyes open but without memory of event)
    - excessive daytime sleepiness

Epidemiology
- 1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems
Etiology
- primary sleep disorders
  - primary insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, periodic limb movements of sleep
- secondary causes
  - medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD, pregnancy, neurological disorders
  - drugs: alcohol, caffeine, nicotine, nicotine replacement therapy, β-agonists, antidepressants, steroids
  - psychiatric: mood and anxiety disorders
  - lifestyle factors: shift work, jet-lag

Investigations
- complete sleep diary every morning for 1-2 wk
  - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (e.g. CBC and differential, TSH)
- refer for sleep study, nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

Treatment of Specific Problems
- primary insomnia
  - majority of cases
  - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
  - treat any suspected medical or psychiatric cause
  - behavior based treatment
    - sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
    - exercise regularly, avoid heavy exercise within 3 h of bedtime
    - relaxation therapy: deep breathing, meditation, biofeedback
    - stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
    - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient (improves sleep efficacy)
    - CBT: address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
  - pharmacologic treatment
    - short-acting benzodiazepines (e.g. lorazepam, oxazepam, temazepam) at the lowest effective dose should be used <7 consecutive nights to break cycle of chronic insomnia or to manage an exacerbation of previously controlled primary insomnia
    - non-benzodiazepines: eszopiclone (Lunesta®), zolpidem (Ambien®), melatonin, low dose anti-depressants with sedating properties (amitriptyline, trazadone, mirtazapine)
    - follow-up every 2-4 wk initially (to reinforce behavioral interventions and renew/consider pharmacotherapy) then every 3 mo; if no progress or limited improvement, consider referral to sleep medicine program
- snoring
  - results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  - physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)
  - treatment
    - sleep on side (position therapy), weight loss
    - nasal dilators (noninvasive external dilator made with elastic adhesive backing applied over nasal bridge), tongue-retaining devices, mandibular advancement devices
  - at risk of developing obstructive sleep apnea
- obstructive sleep apnea (OSA)
  - apnea (no breathing for ≥10 s) resulting from upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present
  - leads to a distinctive snorting, choking, awakening type pattern as the body rouses itself to open the airway (resuscitative breath)
  - apneic episodes can last from 20 s to 3 min and occur 100-600 episodes/night
  - diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes per h of sleep with arousal recorded
  - consequences
    - daytime somnolence, non-restorative sleep
    - poor social and work performance
    - mood changes: anxiety, irritability, depression
    - sexual dysfunction: poor libido, impotence

Risk Factors for Obstructive Sleep Apnea
- 2% of women, 4% of men between ages 30-60
- Obesity (due to upper airway narrowing). BMI >28 kg/m² present in 60-90% of cases
- Children (commonly due to large tonsils and adenoids)
- Aging (due to decreased muscle tone)
- Persistent URIs, allergies, nasal tumors, hypothyroidism (due to macroglia), neuromuscular disease
- Family history
morning headache (due to hypercapnia)
• HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
• pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
• memory loss, decreased concentration, confusion

investigations
• evaluate BP, inspect nose and oropharynx (enlarged adenoids or tonsils)
• blood gas not helpful, TSH if clinically indicated
• nocturnal polysomnography

treatment
• modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
• primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
• surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy, and adenoidectomy (in children)
• report patient to Ministry of Transportation if OSA is not controlled by CPAP

Sore Throat (Pharyngitis)

Definition
• inflammation of the oropharynx
• may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

Etiology
• viral: adenovirus, rhinovirus, influenza virus, RSV, EBV, coxsackie virus, herpes simplex virus, CMV, HIV
• bacterial: group A β-hemolytic Streptococcus (GABHS), group C and group β-hemolytic Streptococcus, Neisseria gonorrhoeae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Corynebacterium diphtheriae

Epidemiology
• viral
  • most common cause (90% in adults is viral), occurs year round
• bacterial
  • GABHS
    • most common bacterial cause
    • occurs most often in winter months
    • 5-15% of adult cases and up to 50% of all pediatric cases of acute pharyngitis
    • most prevalent between 5-17 yr old

Clinical Features
• viral
  • pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  • nonspecific flu-like symptoms such as fever, malaise, and myalgia
  • often mimics bacterial infection
  • EBV (infectious mononucleosis)
    • pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
  • coxsackie virus (hand, foot, and mouth disease)
    • primarily late summer, early fall
    • sudden onset of fever, pharyngitis, headache, abdominal pain, and vomiting
    • appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
    • ulcers are pale gray and several mm in diameter, have surrounding erythema, and may appear on hands and feet
  • herpes simplex virus
    • like coxsackie virus but ulcers are fewer and larger
  • pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
• bacterial
  • symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
  • signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
  • complications: rheumatic fever, glomerulonephritis, suppurative complications (abscess, sinusitis, otitis media, cervical adenitis, pneumonia), meningitis, impetigo

Red Flags in Patients with “Sore Throat”
• Persistence of symptoms longer than 1 wk without improvement
• Respiratory difficulty (particularly stridor, croup, etc.)
• Difficulty in handling secretions (peritonsillar abscess)
• Difficulty in swallowing (Ludwig’s angina)
• Severe pain in the absence of erythema (supraglottitis/epiglottitis)
• Palpable mass (neoplasm)
• Blood in the pharynx or ear (trauma)
Investigations

- suspected GABHS
  - see Table below for approach to diagnosis and management of GABHS
  - gold standard for diagnosis is throat culture
  - rapid test for streptococcal antigen: high specificity (95%) but low sensitivity (50-90%)
  - suspected EBV (infectious mononucleosis)
    - peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or "monospot")

| Table 28. Modified Centor Score: Approach to Diagnosis and Management of GABHS |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| POINTS                          | 1                              | 2                              | 3                              |
| Cough absent?                   | 1                              |                                |                                |
| History of fever > 100.4°F?    | 1                              |                                |                                |
| Tonsillar exudate?             | 1                              |                                |                                |
| Swollen, tender anterior nodes?| 1                              |                                |                                |
| Age 3-14                        | 1                              |                                |                                |
| Age 15-44                       | 0                              |                                |                                |
| Age > 45                        | -1                             |                                |                                |

In communities with moderate levels of strep infection (10-20% of sore throats):

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance patient has strep</td>
<td>1-2.5%</td>
<td>5-10%</td>
<td>11-17%</td>
<td>28-35%</td>
<td>51-53%</td>
</tr>
<tr>
<td>Suggested action</td>
<td>NO culture or antibiotic</td>
<td>Culture all, treat with antibiotics only if culture is positive</td>
<td>Culture all, treat with antibiotics on clinical grounds¹, discontinue antibiotics if culture comes back negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Clinical grounds include a high fever or other indicators that the patient is clinically unwell and is presenting early in the course of the illness

Limitations: *This score is not applicable to patients less than 3 yr of age
* If an outbreak or epidemic of illness caused by GABHS is occurring in any community, the score is invalid and should not be used


Management

- viral pharyngitis
  - antibiotics not indicated
  - symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants

- GABHS
  - antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and suppurative complications
  - incidence of glomerulonephritis is not decreased with antibiotic treatment
  - no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
  - routine F/U and/or post-treatment throat cultures are not required for most patients
  - F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier

- infectious mononucleosis (EBV)
  - self-limiting course; antibiotics are not indicated
  - symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
  - avoid heavy physical activity and contact sports for at least 1 mo or until splenomegaly resolves because of risk of splenic rupture
  - if acute airway obstruction, give corticosteroids and consult ENT
Complementary and Alternative Medicine

Epidemiology
- 50-75% of Americans report some use of CAM over their lifetime, and only half will disclose this use to their physician
- more likely to be used by younger patients and those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy

Herbal Products
- over 50% of Americans use natural health products (NHPs)
- most commonly used include echinacea, ginseng, ginkgo, garlic, St. John's wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  - Are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  - Are you allergic to any plant products?
  - Are you pregnant or breastfeeding?
- information resources: National Center for CAM (www.nccam.nih.gov)

<table>
<thead>
<tr>
<th>Table 29. Common Herbal Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common Name</strong></td>
</tr>
<tr>
<td>Black Cohosh</td>
</tr>
<tr>
<td>Chamomile</td>
</tr>
<tr>
<td>Echinacea</td>
</tr>
<tr>
<td>Evening Primrose</td>
</tr>
<tr>
<td>Feverfew</td>
</tr>
<tr>
<td>Flaxseed Oil</td>
</tr>
<tr>
<td>Garlic</td>
</tr>
<tr>
<td>Ginger</td>
</tr>
<tr>
<td>Ginkgo Biloba</td>
</tr>
<tr>
<td>Ginseng</td>
</tr>
<tr>
<td>Glucosamine (Chondroitin)</td>
</tr>
<tr>
<td>Saw Palmetto</td>
</tr>
<tr>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Valerian Root</td>
</tr>
</tbody>
</table>

### Antimicrobial Quick Reference

<table>
<thead>
<tr>
<th>Condition</th>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATORY/ENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Rhinitis (common cold)</td>
<td>Rhinovirus, coronavirus, influenza, RSV, parainfluenza, adenovirus</td>
<td>None</td>
</tr>
<tr>
<td>Pharyngitis (sore throat)</td>
<td>Rhinovirus, adenovirus, influenza, parainfluenza, coxsackievirus, coronavirus</td>
<td>None</td>
</tr>
<tr>
<td><strong>Strep Pharyngitis</strong></td>
<td>Group A (β-Hemolytic Streptococcus)</td>
<td></td>
</tr>
<tr>
<td><a href="#">Children:</a></td>
<td></td>
<td>1st line: penicillin V 40 mg/kg/d PO div bid-tid (max 750 mg/d) x 10 d (use adult dose if &gt;27 kg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cephalexin 25-50 mg/kg/d PO div qid x 10 d</td>
</tr>
<tr>
<td><a href="#">Adults:</a></td>
<td></td>
<td>1st line: penicillin V 300 mg PO tid or 600 mg bid x 10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefalexin 250 mg PO qid x 10 d</td>
</tr>
<tr>
<td><strong>Sinusitis</strong></td>
<td><strong>S. pneumoniae</strong></td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td><strong>H. influenzae</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>M. catarrhalis</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>S. aureus</strong></td>
<td></td>
</tr>
<tr>
<td><a href="#">Adults:</a></td>
<td></td>
<td>1st line: amoxicillin 500 mg PO tid x 5-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefuroxime-AX 250-500 mg PO bid x 5-10 d</td>
</tr>
<tr>
<td><strong>Acute Otitis Media</strong></td>
<td><strong>S. pneumoniae</strong></td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td><strong>H. influenzae</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>M. catarrhalis</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group A Strep</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>S. aureus</strong></td>
<td></td>
</tr>
<tr>
<td><a href="#">Children:</a></td>
<td></td>
<td>If age 6-24 mo, watchful waiting appropriate if parents can observe child for 48-72 h with appropriate medical follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If age &gt;24 mo, treat if worsens after 48-72 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10 d course if age &lt;24 mo, 5 d course if age &gt;24 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 80 mg/kg/d PO div bid-tid (max 3 g/d) x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d div bid (max 3 g/d) x 10-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td><a href="#">Adults:</a></td>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td><strong>Otitis Externa</strong></td>
<td><strong>P. aeruginosa</strong></td>
<td>1st line: Buro-sol® otic solution 2-3 drops tid or qid</td>
</tr>
<tr>
<td></td>
<td><strong>Coliforms</strong></td>
<td>2nd line: Cortisporin® otic solution 4 drops tid or qid (3 drops tid or qid for children)</td>
</tr>
<tr>
<td></td>
<td><strong>S. aureus</strong></td>
<td>TM defect: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO bid x 4-8 wk</td>
</tr>
<tr>
<td><strong>Bronchitis</strong></td>
<td><strong>H. influenzae, parainfluenza, coronavirus, rhinovirus, RSV</strong></td>
<td>None</td>
</tr>
<tr>
<td>Condition</td>
<td>Microorganisms</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>-----------</td>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td><strong>Community Acquired Pneumonia: Outpatient without Comorbidity</strong></td>
<td><em>S. pneumoniae</em>, <em>M. pneumoniae</em>, <em>C. pneumoniae</em></td>
<td>1st line: amoxicillin 1,000 mg PO tid x 7-14 d (for patients over age 50 where mycoplasma infection is less likely) erythromycin 500 mg PO qid x 7-14 d clari-thromycin 500 mg PO bid or 1,000 mg (ER) PO OD x 7-14 d azithromycin 500 mg PO on 1st d then 250 mg PO OD x 4 d or 500 mg PO OD x 3 d 2nd line: doxycycline 100 mg PO on 1st d then 100 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td><strong>Community Acquired Pneumonia: Outpatient with Comorbidity</strong></td>
<td><em>S. pneumoniae</em>, <em>M. pneumoniae</em>, <em>C. pneumoniae</em>, <em>H. influenzae</em></td>
<td>ANY ONE of the β-lactam agents below: amoxicillin 1,000 mg PO tid x 7-14 d amoxicillin/clavulanate 500 mg PO tid or 875 mg PO bid x 7-14 d cefuroxime-AX 500 mg PO bid x 7-14 d cefprozil 500 mg PO bid x 7-14 d PLUS ONE of the following: clari-thromycin 500 mg PO bid or 1,000 mg (ER) PO OD x 7-14 d azithromycin 500 mg PO OD on 1st d then 250 mg PO OD x 3 d doxycycline 100 mg PO bid on 1st d then 100 mg PO OD x 7-14 d OR ANY ONE of the following: levofloxacin 750 mg PO OD x 7-14 d moxifloxacin 400 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td><strong>Dental Infections/Periapical and Periodontal Abscesses</strong></td>
<td>Oral Flora</td>
<td>penicillin V potassium 500 mg PO qid x 7-10 d clindamycin 300 mg PO qid or 600 mg bid x 7-10 d</td>
</tr>
<tr>
<td><strong>GASTROENTEROLOGY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea – Enteritis</strong></td>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>Mild to moderate (i.e. &lt;3 BM/d, no blood, no fever): OTC loperamide 4 mg PO STAT then 2 mg PO after each loose stool (max 8 doses/d) OTC bismuth subsalicylate (Pepto Bismol®) 2 tabs or 30 mL repeat q30min pm (max 8 doses/d) (prevention: 2 tabs or 30 mL qid with meals and in the evening) Moderate to severe (i.e. &gt;3 BM/d, blood, fever): ofloxacin 400 mg PO single dose or 300 mg PO bid x 3 d (prevention: 300 mg PO OD) norfloxacin 800 mg PO single dose or 400 mg PO bid x 1-3 d (prevention: 400 mg PO OD) ciprofloxacin 750 mg PO single dose or 500 mg PO bid x 1-3 d (prevention: 500 mg PO OD) levofloxacin 500 mg PO OD x 1-3 d (prevention: 500 mg PO OD) azithromycin 1,000 mg PO single dose or 500 mg PO OD x 1-3 d (children: 10 mg/kg/d x 3 d) Azithromycin: Recommended primarily for Thailand, India, Nepal, and Indonesia where Campylobacter resistance to quinolones is high Considered drug of choice for children because of safety, tolerability, and ease of administration</td>
</tr>
<tr>
<td><strong>Diarrhea – Post Abx (common with clindamycin)</strong></td>
<td><em>C. difficile</em></td>
<td>Mild to moderate (WBC &lt;5 x 10⁹/L and Cr &lt;1.5 x baseline): metronidazole 500 mg PO tid or 250 mg PO qid x 10 d (children: 15-30 mg/kg/d PO div tid-qid max 4 g/d) Severe (WBC ≥15 x 10⁹/L and Cr ≥1.5 x baseline): vancomycin 125 mg PO qid x 10-14 d (children: 40 mg/kg/d PO div tid-qid x 10-14 d max 2 g/d)</td>
</tr>
<tr>
<td><strong>Peptic Ulcer Disease (non-NSAID related)</strong></td>
<td><em>H. pylori</em></td>
<td>PPI: lansoprazole 30 mg or omeprazole 20 mg or pantoprazole 40 mg or rabeprazole 20 mg 1st line: (PPI PO bid + amoxicillin 1,000 mg PO bid + clarithromycin 500 mg PO bid x 7 d) (e.g. HP-PAC: lansoprazole 30 mg PO bid + amoxicillin 1,000 mg PO bid + clarithromycin 500 mg PO bid x 7 d) 2nd line: (PPI PO bid + metronidazole 500 mg PO bid + clarithromycin 500 mg or 250 mg PO bid x 7 d) (PPI PO bid + metronidazole 500 mg PO bid + clarithromycin 500 mg or 250 mg PO bid x 7 d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(PPI PO bid + bismuth subsalicylate 2 tabs or 30 mL qid + metronidazole 250 mg PO qid + tetracycline 500 mg PO qid x 7-14 d)</td>
</tr>
</tbody>
</table>
## GENITOURINARY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI/Cystitis</td>
<td>Klebsiella</td>
<td>1st line: TMP/SMX 2 tabs bid or 1 DS tab bid x 3 d</td>
</tr>
<tr>
<td></td>
<td>E. coli</td>
<td>trimethoprim 100 mg PO bid or 200 mg PO OD x 3 d</td>
</tr>
<tr>
<td></td>
<td>Enterobacter</td>
<td>nitrofurantoin 50-100 mg PO qid or Macrolide® 100 mg bid x 5 d</td>
</tr>
<tr>
<td></td>
<td>Enterococci</td>
<td>2nd line: amoxicillin 500 mg PO tid x 7 d</td>
</tr>
<tr>
<td></td>
<td>Proteus</td>
<td>norfloxacin 400 mg PO bid x 3 d</td>
</tr>
<tr>
<td></td>
<td>S. saprophyticus</td>
<td>ciprofloxacin 250 mg PO bid or 500 mg (ER) OD x 3 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB: high rate of amoxicillin resistance in community E. coli, use only after lab susceptibility obtained</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cephalexin 250-500 mg PO qid x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>levofloxacin 250 mg PO OD x 3 d</td>
</tr>
<tr>
<td>Pregnancy:</td>
<td></td>
<td>cephalexin 250-500 mg PO qid x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nitrofurantoin 50-100 mg PO bid x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>amoxicillin 500 mg PO tid x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NB: nitrofurantoin is contraindicated in pregnancy after 36 wk</td>
</tr>
</tbody>
</table>

### Head and Pubic Lice (crabs)

<table>
<thead>
<tr>
<th>Vulvovaginal Candidiasis</th>
<th>Pediculus humanus capitis</th>
<th>permethrin cream 1%: apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phthirus pubis</td>
<td>Treat only if patient is symptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluconazole 150 mg PO single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>micronazole 2% cream (Monistat 7®): one applicator (5 g) intravaginally qhs x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>multiple other OTC azole treatments</td>
</tr>
</tbody>
</table>

### Bacterial Vaginosis

<table>
<thead>
<tr>
<th>Overgrowth of:</th>
<th>G. vaginalis</th>
<th>If patient is asymptomatic, treatment is unnecessary unless high-risk pregnancy, prior IUD insertion, gynecologic surgery, induced abortion, or upper tract instrumentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. hominis</td>
<td></td>
<td>1st line: metronidazole 500 mg PO bid x 7 d</td>
</tr>
<tr>
<td>Anaerobes</td>
<td></td>
<td>metronidazole 0.75% gel: one applicator (5 g) intravaginally qhs x 5 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin 2% cream: one applicator (5 g) intravaginally qhs x 7 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: metronidazole 2 g PO single dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clindamycin 300 mg PO bid x 7 d</td>
</tr>
</tbody>
</table>

### Herpes

| Herpes simplex virus     | 1° episode: acyclovir 400 mg PO tid x 5-7 d |
|                         | famciclovir 250 mg PO od x 5-7 d |
|                         | valacyclovir 500-1,000 mg PO bid x 5-7 d |
| Recurrent Episode:      | acyclovir 400 mg PO tid x 5 d or 800 mg PO bid x 5 d or 800 mg PO tid x 2 d |
|                         | famciclovir 125 mg PO bid x 5 d |
|                         | valacyclovir 500 mg PO bid x 3 d or 1,000 mg PO OD x 3 d |
| Pregnancy:              | 1° episode: acyclovir 200 mg PO 5x/d x 5-10 d |
|                         | Prior infection within previous yr: acyclovir 200 mg PO qid at 36 wk |
|                         | valacyclovir 500 mg PO bid at 36 wk |

### Gonorrhea/Chlamydia

| N. gonorrhoeae | C. trachomatis | ceftriaxone 250 mg IM x 1 dose + azithromycin 1 g PO |
|               |                | single dose or doxycycline 100 mg PO bid x 7 d |

## DERMATOLOGIC

### Mastitis

| S. aureus | cloxacillin 500 mg PO qid x 7 d |
| S. pyogenes | cephalixin 500 mg PO qid x 7 d |

### Tinea Cruris/Pedis (jock itch/athlete’s foot)

| Trichophyton | clotrimazole 1% cream bid |
|             | ketoconazole 2% cream bid |

### Uncomplicated Cellulitis

<table>
<thead>
<tr>
<th>S. aureus</th>
<th>Group A Streptococcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children:</td>
<td>1st line: cephalexin 50-100 mg/kg/d div qid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td>2nd line: cloxacillin 50 mg/kg/d div qid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td>clindamycin 25 mg/kg/d x 10-14 d</td>
</tr>
<tr>
<td>Adults:</td>
<td>1st line: cephalexin 500 mg PO qid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td>2nd line: cephalexin 500 mg PO qid x 10-14 d</td>
</tr>
<tr>
<td></td>
<td>clindamycin 300 mg PO x 10-14 d</td>
</tr>
</tbody>
</table>

*All doses are adult doses unless otherwise specified
*This chart is not all-encompassing and is non-inclusive of special exceptions (i.e. pregnancy, poor renal clearance, etc.)
*Comorbidities include: COPD (received steroids within the last 3 mo), liver or renal disease, CHF, DM, malignancy, alcoholism, aspernia, immunosuppressing conditions, malnutrition, hospitalization in past 3 mo or nursing home
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Alcoholic Liver Disease
Non-Alcoholic Fatty Liver Disease
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Overview of Gastrointestinal Tract

• the gastrointestinal tract runs from mouth to anus ("gum to bum")

Table 1. Summary of Gastrointestinal Tract Structure and Function

<table>
<thead>
<tr>
<th>Organ</th>
<th>Function</th>
<th>Blood Supply</th>
<th>Innervation</th>
<th>Histology and Structural Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>• Muscular tube approximately 25 cm long with a diameter of 2 cm</td>
<td>• Arterial: left gastric artery and left inferior phrenic artery</td>
<td>• Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks)</td>
<td>• Mucosa: stratified squamous epithelium</td>
</tr>
<tr>
<td></td>
<td>• Extends from pharynx to the stomach</td>
<td>• Venous: Left gastric vein → portal venous system</td>
<td>• Sympathetic innervation via thoracic trunks of the greater splanchnic nerves</td>
<td>• Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Esophageal veins → aygos vein → IVC (systemic)</td>
<td></td>
<td>• Muscularis propria (muscularis externa): inner circular, outer longitudinal muscle</td>
</tr>
<tr>
<td>Stomach</td>
<td>• Delivers food to intestine for digestion and absorption</td>
<td>• Lesser curvature:</td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>• 5 parts:</td>
</tr>
<tr>
<td></td>
<td>• Secretes acid, probably to reduce enteric infections/pneumonia; facilitate digestion of protein/iron/B₁₂</td>
<td>• Right and left gastric arteries (from celiac trunk)</td>
<td>• Sympathetic innervation via celiac plexus (from T6-T9)</td>
<td>• Cardia</td>
</tr>
<tr>
<td></td>
<td>• Secretes intrinsic factor to facilitate B₁₂ absorption</td>
<td>• Greater curvature:</td>
<td></td>
<td>• Fundus</td>
</tr>
<tr>
<td></td>
<td>• Minor contribution to initial protein digestion via pepsin</td>
<td>• Right and left gastroesophageal (gastroepiploic) arteries (from gastroduodenal and splenic a. respectively)</td>
<td></td>
<td>• Body</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Fundus: short and posterior gastric arteries (from the splenic artery)</td>
<td></td>
<td>• Antrum</td>
</tr>
<tr>
<td>Duodenum</td>
<td>• Modulates enteral pH via secretin → decreased gastric acid secretion; increased bicarbonate secretion</td>
<td>• Branches of celiac artery and superior mesenteric artery</td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>• Pylorus</td>
</tr>
<tr>
<td></td>
<td>• Secretes CCK to stimulate bile secretion</td>
<td>• Parasympathetic innervation via greater and lesser splanchnic nerves</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 1. Summary of Gastrointestinal Tract Structure and Function (continued)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Function</th>
<th>Blood Supply</th>
<th>Innervation</th>
<th>Histology and Structural Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunum</td>
<td>• Absorption of sodium, water, and nutrients (protein, carbohydrates, fat, folic acid, and vit A, B, C, D, E, K)</td>
<td>• Superior mesenteric artery</td>
<td>• Parasympathetic innervation via fibers of the posterior vagal trunk</td>
<td>• Deep red color&lt;br&gt; • 2-4 cm in thickness&lt;br&gt; • Thick and heavy wall&lt;br&gt; • Plicae circulars are large, tall and closely packed&lt;br&gt; • Has long vasa recta&lt;br&gt; • Scant fat in mesentery&lt;br&gt; • Scant Peyer’s patches</td>
</tr>
<tr>
<td>Ileum</td>
<td>• Absorption of sodium, water, nutrients, soluble vitamins (only site of vit B₁₂ absorption), and bile salt (entero-hepatic circulation)</td>
<td>• Superior mesenteric artery</td>
<td>• Same as jejunum</td>
<td>When compared to jejunum:&lt;br&gt; • Paler pink color&lt;br&gt; • 2-3 cm in thickness&lt;br&gt; • Thin and light walls&lt;br&gt; • Plicae circulars are small and sparse&lt;br&gt; • Contains more mesenteric fat&lt;br&gt; • Many Peyer’s patches</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>• Absorption of water (5-10% of total water)</td>
<td>• Branches of superior and inferior mesenteric arteries</td>
<td>• Parasympathetic innervation via vagus nerve&lt;br&gt; • Sympathetic innervation via greater and lesser splanchnic nerves</td>
<td>• Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal&lt;br&gt; • Features include tentiae coli, haustra, and omental appendices</td>
</tr>
<tr>
<td>Liver</td>
<td>• Glucose homeostasis&lt;br&gt; • Plasma protein synthesis&lt;br&gt; • Lipid and lipoprotein synthesis&lt;br&gt; • Bile acid synthesis and secretion&lt;br&gt; • Vitamin A, D, E, K, B₁₂, B₂₁₂, D, E, K storage&lt;br&gt; • Biotransformation, detoxification&lt;br&gt; • Excretion of compounds</td>
<td>• 2 sources&lt;br&gt; • Portal vein (75-80%)&lt;br&gt; • Hepatic artery (20-25%)</td>
<td>• Sympathetic innervation via fibers of the celiac plexus&lt;br&gt; • Parasympathetic innervation via fibers of the anterior and posterior vagal trunks</td>
<td>• Largest internal organ&lt;br&gt; • Composed of 4 lobes (left, right, caudate, quadrate) and divided into 8 segments</td>
</tr>
<tr>
<td>Biliary Tract</td>
<td>• Gallbladder functions to store and release bile that is produced in the liver&lt;br&gt; • Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids, and bilirubin&lt;br&gt; • CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release</td>
<td>• Cystic artery</td>
<td>• Parasympathetic innervation via vagus nerve&lt;br&gt; • Sympathetic and visceral innervation via celiac nerve plexus&lt;br&gt; • Somatic afferent fibers via right phrenic nerve</td>
<td>• Consists of the hepatic ducts (intrahepatic, left, right and common), gallbladder, cystic duct, common bile duct, and ampulla of Vater&lt;br&gt; • Accessory pancreatic duct connecting to common bile duct prior to ampulla of Vater</td>
</tr>
<tr>
<td>Pancreas</td>
<td>• Endocrine function: islets of Langerhans produce glucagon, insulin, and somatostatin (from the α, β, and δ cells, respectively)&lt;br&gt; • Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase</td>
<td>• Anterior superior pancreaticoduodenal artery (from the celiac trunk)&lt;br&gt; • Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery)&lt;br&gt; • Dorsal pancreatic artery (from the splenic artery)&lt;br&gt; • Pancreatic veins drain into the portal, splenic, and superior mesenteric veins</td>
<td>• Parasympathetic innervation via vagus nerve&lt;br&gt; • Sympathetic innervation via abdominal pelvic splanchnic nerves</td>
<td>• 4 parts of pancreas: head (includes uncinate process), neck, body, and tail&lt;br&gt; • (Major) pancreatic duct connecting to common bile duct prior to ampulla of Vater&lt;br&gt; • Accessory pancreatic duct connected directly to duodenum</td>
</tr>
</tbody>
</table>

**Visualizing the Gastrointestinal Tract**

- see Medical Imaging, MI10

**Esophagus, Stomach, Duodenum**

- OGD: best visualization of mucosa; also allows for therapeutic intervention (e.g. banding varices, thermal therapy/clipping/injecting bleeding ulcers, and dilatation e.g. esophageal strictures)
  - consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation)<br>  - endotracheal intubation first if massive upper GI bleed, acidemia, or inability to protect airway
Small Bowel
- most difficult to visualize, especially if mucosal detail is needed
- CT enterography more accurate than small bowel follow through, but both have low sensitivity
- MRI enterocolonoscopy increasingly available (use enterocolonoscopy if dilatation of the small bowel might improve sensitivity, such as diverticulosis, or if stricture suspected)
- "double balloon" enteroscopy (enteroscope with proximal and distal balloons to propel endoscope into jejunum from mouth or into jejunum/ileum or into ileus from anus) may be most sensitive but currently available only in selected centers; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction) is also accurate in diagnosis but unable to provide any therapeutic intervention

Colon and Terminal Ileum
- colonoscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis, and severe colitis (increased risk of perforation)
- CT colonography ("virtual colonoscopy") more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), and fistulae; increasing evidence for use in colorectal cancer screening, especially for assessment of right side of colon in cases where colonoscopy is incomplete

Pancreatic/Biliary Duct
- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumor, stone, stricture)
- ERCP if endoscopic draining necessary, strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required

Differential Diagnosis of Common Presenting Complaints

Table 2. Differential Diagnosis of Common Presenting Complaints

<table>
<thead>
<tr>
<th>ACUTE ABDOMINAL PAIN</th>
<th>Upper/Mid-Abdomen</th>
<th>Lower Abdomen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td>Gastroenteritis</td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Appendicitis</td>
<td></td>
</tr>
<tr>
<td>Perforated peptic ulcer</td>
<td>Diverticulitis</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Crohn's disease</td>
<td></td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>Pelvic inflammatory disease</td>
<td></td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>Eclectic pregnancy</td>
<td></td>
</tr>
<tr>
<td>Ruptured aortic aneurysm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHRONIC/RECURRENT ABDOMINAL PAIN</th>
<th>Inflammatory</th>
<th>Neoplastic/Vascular</th>
<th>Toxin</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUD</td>
<td>Recurrent bowel obstruction</td>
<td>Lead poisoning</td>
<td>Mittelschmertz</td>
<td>Endometriosis</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Recurrent bowel obstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>Mesenteric ischemia</td>
<td></td>
<td></td>
<td>IBS</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Sickle cell anemia</td>
<td></td>
<td>Exocrine</td>
<td>Radiopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE DIARRHEA</th>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Protozal</td>
<td>Viral</td>
</tr>
<tr>
<td>Shigella*</td>
<td><em>E. histolytica</em></td>
<td>Rotavirus</td>
</tr>
<tr>
<td>Salmonella*</td>
<td>(amoebiasis)</td>
<td>Nonwalk</td>
</tr>
<tr>
<td>Campylobacter*</td>
<td>Strongyloides</td>
<td></td>
</tr>
<tr>
<td>Yersinia*</td>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td>E. coli (EHEC)</td>
<td>* Others</td>
<td></td>
</tr>
<tr>
<td>0157:H7*</td>
<td>NSAIDs</td>
<td></td>
</tr>
<tr>
<td>C. difficile</td>
<td>IBD*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ischemic*</td>
<td></td>
</tr>
</tbody>
</table>

*Causes of bloody diarrhea

Acute Upper Abdominal Pain
Remember to rule out thoracic sources, e.g. myocardial infarction, pneumonia, dissecting aneurysm

Obscure But Treatable Causes of Abdominal Pain
- Porphyria
- Angioedema
- Familial Mediterranean Fever
- Vasculitis (e.g. polyarteritis nodosa)

Rule out IBD when patient presents with bloody diarrhea
### Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

<table>
<thead>
<tr>
<th>CHRONIC DIARRHEA</th>
<th>(A) Organic</th>
<th>Steatorrheic</th>
<th>Osmotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Causes of bloody diarrhea</em></td>
<td>IBD</td>
<td>Stimulant laxatives</td>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Infecetious (C. difficile, TB, CMV, HSV)</td>
<td>Infectious</td>
<td>Post-ileal resection/cholecystectomy (bile salts)</td>
<td>Celiac sprue</td>
</tr>
<tr>
<td>Ischemic bowel</td>
<td>Bacterial toxins</td>
<td>Chronic pancreatitis</td>
<td>Chronic cholestasis</td>
</tr>
<tr>
<td>Radiation colitis</td>
<td>Vasculitis</td>
<td>Neoplasm (Colon Ca, Carcinoid, VIPoma)</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Neoplasia (Colon Ca, Carcinoid, VIPoma)</td>
<td>Addison’s disease</td>
<td>Congenital syndromes</td>
</tr>
</tbody>
</table>

#### CONSTIPATION: if no associated rectal bleeding/weight loss, etc., usually no cause found

| | Cologrectal cancer | Medications (narcotics, antidepressants, calcium channel blockers) | Neurologic (Parkinson’s, MS, stroke) |
| | Stricture | Metabolic (DM, thyroid, hypercalceemia) | Gastrovascular disease (scleroderma, dermatomyositis) |
| | Extrinsics compression | | |
| | Anal disease | | |
| | Rectocle | | |

#### NAUSEA/ VOMITING

| | With Abdominal Pain | Without Abdominal Pain | Headache/Dizziness | No Other Symptoms |
| | Relieved by Vomiting | Not Relieved by Vomiting | | |
| Gastric outlet obstruction | Gallbladder disease | Pancreatitis | Cerebral tumor | Drugs |
| Small bowel obstruction | Myocardial infarction | Hepatitis | Migrane | Uremia |
| GERD (regurgitation more common) | Infectious | Gastroenteritis | Vestibular disease | Pregnancy |
| | | | Increased ICP | Metabolic (e.g. hypercalceemia) |

#### DYSPEPSIA

| | Common | Uncommon | Rare |
| | Functional dyspepsia | Angina | Giardia lamblia |
| | Drug side effect | Crohn’s disease | Malabsorption (celiac sprue) |
| | Peptic ulcer | Cancer | |
| | GERD | Gallstones | Aerophagia |

#### UPPER GI BLEED

| | Common | Uncommon | Rare |
| | Ulcers (H. pylori, ASA, NSAIDs) | Tumors | Aorto-enteric fistulas |
| | Esophageal varices | Arteriovenous malformation | Hemobilia |
| | Mallory-Weiss tears | Dieulafoy’s lesion (arterial) | |
| | Erosive esophagitis | Gastric antral vascular ectasia (GAVE) | |
| | Erosive gastritis | Portal hypertensive gastropathy | |

#### LOWER GI BLEED

| | Common | Uncommon | Rare |
| | Diverticulosis | Upper GI bleed (brisk) | Intussusception |
| | Ischemia | Post-polyectomy | Vascuditides |
| | Angiodyplasia (elderly) | Radiation colitis | Stercoral ulcer |
| | Infectious | IBD | Coagulopathies |
| | Anorectal (hemorrhoids, fissure, ulcer) | | |

#### DYSPHAGIA

| | Mechanical (Solids) | Motility (Solids and Liquids) | Other |
| | Peptic stricture/cancer | Achalasia | Foreign body |
| | Eosinophilic esophagitis | Diffuse esophageal spasm | Esophogiphilic esophagitis |
| | Extrinsic compression | Scleroderma | |
| | Schatzki ring/esophageal web | | |
| | Zenker’s diverticulum | | |
Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

<table>
<thead>
<tr>
<th>ODYNOPHAGIA</th>
<th>Infection</th>
<th>Inflammation/Ulceration</th>
<th>Drugs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candida</td>
<td>Caustic damage</td>
<td>Quinidine</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Herpes</td>
<td>Eosinophilic esophagitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CMV (common in those who are immunosuppressed)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ABDOMINAL DISTENTION</th>
<th>Fluid (Ascites)</th>
<th>Flatulence</th>
<th>Feces</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Portal HTN</td>
<td>Normal Portal Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Cancer (especially ovarian)</td>
<td>Functional bowel disease (e.g. IBS)</td>
<td>Constipation (e.g. red blood cells)</td>
<td>Pregnancy (e.g. fetus)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Pancreatitis TB</td>
<td>Fiber</td>
<td>Colon obstruction</td>
<td>Obesity (fat)</td>
</tr>
<tr>
<td>Hepatic vein thrombosis</td>
<td>Lactose intolerance</td>
<td>Chewing gum (e.g. sorbitol, mannitol)</td>
<td>Dysmotility</td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Large tumors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(fatal growth)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>JAUNDICE (UNCONJUGATED BILIRUBIN)</th>
<th>Overproduction</th>
<th>Decreased Hepatic Intake</th>
<th>Decreased Conjugation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
<td>Gilbert’s syndrome</td>
<td>Drug inhibition (e.g. chloramphenicol)</td>
<td></td>
</tr>
<tr>
<td>Ineffective erythropoiesis (e.g. megaloblastic anemias)</td>
<td>Drugs (e.g. rifampin)</td>
<td>Crigler-Najjar syndromes type I and II</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gilbert’s syndrome</td>
<td>Neonatal jaundice</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>JAUNDICE (CONJUGATED BILIRUBIN)</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular disease</td>
<td>Intraductal obstruction</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>Gallstones</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis (any cause)</td>
<td>Biliary stricture</td>
<td></td>
</tr>
<tr>
<td>Inflammation (hepatitis, any cause)</td>
<td>Parasites</td>
<td></td>
</tr>
<tr>
<td>Infiltrative (e.g. hemochromatosis)</td>
<td>Malignancy (cholangiocarcinoma)</td>
<td></td>
</tr>
<tr>
<td>Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy)</td>
<td>Sclerosing cholangitis</td>
<td></td>
</tr>
<tr>
<td>PBC</td>
<td>Extrabiliary obstruction</td>
<td></td>
</tr>
<tr>
<td>PSC</td>
<td>Malignancy (e.g. pancreatic cancer, lymphoma)</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>Metastases in periportal nodes</td>
<td></td>
</tr>
<tr>
<td>Post-operative/TPN</td>
<td>Inflammation (e.g. pancreatitis)</td>
<td></td>
</tr>
</tbody>
</table>

**Esophagus**

**Gastroesophageal Reflux Disease**

**Definition**
- condition in which the stomach contents (most characteristically acid) moves backwards from the stomach into the esophagus (the tube from the mouth to the stomach)

**Etiology**
- inappropriate transient relaxations of LES – most common cause
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, obesity, pregnancy
- acid hypersecretion (rare): Zollinger-Ellison syndrome (gastrin-secreting tumor)
- hiatus hernia worsens reflux, does not cause it (see General Surgery, GS12)

**Clinical Features**
- "heartburn" (pyrosis) and acid regurgitation (together are 80% sensitive and specific for reflux) ± sour regurgitation, water brash, sensation of a lump in the throat (bolus sensation), and frequent belching
- non-esophageal symptoms (see G7) are increasingly recognized of being poor predictors of reflux

**Foods/Substances that Aggravate GERD Symptoms**
- EtOH
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices

**Epigastric discomfort** = postprandial fullness, early satiety, epigastric pain, or burning
GERD signs/symptoms

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Chronic cough</th>
<th>Wheezing</th>
<th>Aspiration pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-respiratory</td>
<td>Sore throat</td>
<td>Hoarseness</td>
<td>Dental erosions</td>
</tr>
<tr>
<td>Typical Heartburn</td>
<td>Acid regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Chest pain</td>
<td>Dysphagia (late)</td>
<td>Odynophagia (rare)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Signs and symptoms of GERD

Investigations
- Usually a clinical diagnosis based on symptom history and relief following a trial of pharmacotherapy (PPI: symptom relief 80% sensitive for reflux)
  - Absolute indications:
    - Heartburn accompanied by red-flags (bleeding, weight loss, etc.)
    - Persistent reflux symptoms or prior severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI 2x daily
    - History of esophageal stricture with persistent dysphagia
- Repeat endoscopy indicated only if known Barrett’s (or recurrence of symptoms) because future likelihood of Barrett’s and esophagitis is minimal if the first endoscopy is normal
- Esophageal manometry (study of esophageal motility)
- May be done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to intact esophageal function
- Surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus) more likely to be successful if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- 24 h pH monitoring: most accurate test, but not required or performed in most cases
  - Most useful if PPIs do not improve symptoms

Management
- PPIs are the most effective therapy and usually need to be continued as maintenance therapy
- On-demand: antacids (Mg(OH)2, Al(OH)3, alginate), H2-blockers, or PPIs can be used for NERD
- Diet helps symptoms, not the disease; avoid alcohol, coffee, spices, tomatoes, and citrus juices
- Only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)
- Dyspepsia may recur if therapy is discontinued

Complications
- Esophageal stricture disease – scarring can lead to dysphagia (solids)
- Ulcer
- Bleeding
- Barrett’s esophagus and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

Barrett’s Esophagus

Definition
- Metaplasia of normal squamous esophageal epithelium to abnormal columnar epithelium containing-type intestinal mucosa (intestinal metaplasia)

Etiology
- Thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Epidemiology
- In North America and Western Europe, 0.5-2.0% of adults are thought to have Barrett’s esophagus
- Up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- More common in males, age >50, Caucasians, smokers, overweight, hiatus hernia, and long history of reflux symptoms

Pathophysiology
- Endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes to premalignant changes in abnormal columnar epithelium, characterized as low- or high-grade dysplasia

Screening and surveillance are critical as dysplasia, which is the most feared complication of BE, carries a variable risk of progression to adenocarcinoma.


diagram: Classification of gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD)
- Non-erosive reflux disease (NERD)
- Normal esophagus
- Aim for symptom relief only; proton pump inhibitor (PPI)

Esophagitis
- Esophageal inflammation
- Aim to heal inflammation; proton pump inhibitor indefinitely or surgical fundoplication

Up to 25% of patients with Barrett’s esophagus do not report symptoms of GERD

Updated Guidelines 2008 for the Diagnosis, Surveillance, and Therapy of Barrett’s Esophagus
- Screening of the general population is not recommended and needs to be individualized based on risk factors. Role of esophageal capsule endoscopy for screening is currently under investigation.
- Surveillance interval is based on grade of dysplasia. If no dysplasia confirmed on two endoscopies within a year, then q3yr. For low-grade dysplasia (LGD), repeat endoscopy within 6 mo to ensure there is no high-grade dysplasia (HGD) and if none, then q6yr until no dysplasia on two consecutive endoscopies. If HGD, repeat endoscopy within 3 mo to ensure there is no adenocarcinoma and recommend intervention (endoscopic resection) or intensive surveillance (endoscopy q3mo).
- Diagnosis using alternative imaging techniques (fiberoptic, chromoendoscopy) and biomarkers (DNA content abnormalities, loss of heterozygosity or methylation of specific genes) are being investigated but none are currently ready for routine clinical use.
- Treatment of reflux symptoms with PPI decreases the development of dysplasia. Surgery (fundoplication) for patients without major comorbidities and whose reflux symptoms are controlled on PPI has a 20% failure rate at 5 yr and has not shown to decrease progression to adenocarcinoma.
- Prognosis: 5-yr risk of esophageal adenocarcinoma in high-grade dysplasia is >30%.
- Management in high-grade dysplasia, surveillance with intensive biopsy, endoscopic ablation, or esophagectomy produce similar outcomes and thus should be individualized to patient preference and local expertise.
Significance
• rate of malignant transformation is approximately 0.12% per yr for all BE patients prior to dysplasia
• risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance
• increased gastric acid secretion is more frequently associated with Barrett’s esophagus as opposed to reflux alone

Management
• acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication)
• endoscopy every 3 yr if no dysplasia
• high grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes; however, evidence increasingly favoring endoscopic ablation with mucosal resection or radiofrequency ablation
• if low grade dysplasia, both surveillance and endoscopic ablation/resection are satisfactory options

Dysphagia
Definition
• difficulty swallowing, globus sensation

Esophageal Motor Disorders
Symptoms
• dysphagia with solids and liquids
• chest pain (in some disorders)

Diagnosis
• motility study (esophageal manometry)
• barium swallow sometimes helpful

Causes (Table 3)
• idiopathic
• achalasia (painless)
• scleroderma (painless)
• DM
• DES: rare and can be difficult to diagnose due to intermittent presentation
Table 3. Esophageal Motor Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Achalasia</th>
<th>Scleroderma</th>
<th>Diffuse Esophageal Spasm</th>
</tr>
</thead>
</table>
| **Definition**  | • Failure of smooth muscle relaxation at LES  
• Increased LES pressure  
• Progressive loss of peristaltic function  
See Rheumatology, RH13  
• Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening)  
• Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis) |
| **Etiology**    | • Usually idiopathic  
• 2° or pseudo-achalasia: e.g. malignancy, Chagas disease (Trypanosoma cruzi)  
• Involves autoimmune, genetic, hormonal, and environmental factors  
• Dysphagia: caused by reflux, dysmotility, or both |
| **Pathophysiology** | • Inflammatory degeneration of Auerbach’s plexus  
• Blood vessel damage  
• Incomplete relaxation of LES with swallowing, aperistalsis  
• Intramural neuronal dysfunction  
• Distal esophageal muscle weakening  
• Aperistalsis and loss of LES tone  
• Reflux  
• Stricture  
• Dysphagia  
• Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis |
| **Diagnosis**   | • CXR: no air in stomach, dilated esophagus  
• Barium studies: esophagus terminates in narrowing at LES (“bird’s beak”)  
• Endoscopy: rule out malignancy  
• Manometry: definitive diagnosis (signs listed above)  
• Clinical features of scleroderma  
• Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus  
• Barium x-ray: “Corkscrew pattern”  
• Manometry: >30% (but <100%) of esophageal contractions are aperistaltic |
| **Treatment**   | • Dilatation of LES with balloon, ± GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%)  
• Injection of botulinum toxin into LES (temporary)  
• Surgery (myotomy)  
• Medical: aggressive GERD therapy (PPIs bid)  
• Surgery: anti-reflux surgery (gastroplasty, last resort)  
• Reassurance not cardiac pain  
• Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit  
• Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful); balloon dilatation |

**Esophageal Diverticula**

**Definition**
- outpouchings of one or more layers of the esophageal tract

**Clinical Features**
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

**Classification**
- classified according to location
  - pharyngoesophageal (Zenker’s) diverticulum
    - most frequent form of esophageal diverticulum
    - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
    - symptoms: dysphagia, regurgitation of undigested food, halitosis
    - treatment: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac
  - mid-esophageal diverticulum
    - secondary to mediastinal inflammation, motor disorders
    - usually asymptomatic; no treatment required
    - just proximal to LES (pulsatile type)
    - usually associated with motor disorders
    - usually asymptomatic; no treatment required

**Peptic Stricture (from Esophagitis)**
- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

**Treatment**
- endoscopic dilatation and indefinite PPI
- anti-reflux surgery if above treatment unsuccessful
**Esophageal Carcinoma**

- see [General Surgery, GS14](#)

**Webs and Rings**

- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

**Clinical Features**

- asymptomatic with lumen diameter > 12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Schatzki ring
  - mucosal ring at squamo-columnar junction above a hiatus hernia
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic bougie

**Infectious Esophagitis**

**Definition**

- severe mucosal inflammation and ulceration as a result of a viral or a fungal infection

**Risk Factors**

- DM
- chemotherapeutic agents
- immunocompromised states

**Symptoms**

- characteristically odynophagia, less often dysphagia
- diagnosis is via endoscopic visualization and biopsy

**Appearance**

- Candida (most common): whitish-yellow plaques without visible ulceration or inflammation
- Herpes (second most common), CMV: focal ulcers

**Treatment**

- Candida: nystatin swish and swallow, ketoconazole, fluconazole
- Herpes: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV gancyclovir, famciclovir, or oral valganciclovir

**Stomach and Duodenum**

**Dyspepsia**

**Definition**

- intermittent epigastric discomfort, characteristically develops after eating

**History and Physical**

- history: most important are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical exam: adenopathy, abdominal mass/organomegaly, Carnett’s sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

**Investigations**

- laboratory: usual (CBC, liver enzymes, glucose, Cr, etc.) plus amylase, albumin
- consider trial of empiric anti-secretory drug therapy, non-invasive testing for *H. pylori* infection, endoscopy, barium radiography
Gastric Acid Secretion

Stomach
- primary function is mechanical grinding of food facilitating early enzymatic digestion into chyme and propulsion into duodenum

Table 4. Cells of the Gastric Mucosa

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Secretory Product</th>
<th>Important Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parietal cells</td>
<td>Gastric acid (HCl) Intrinsic factor</td>
<td>Stimulated by histamine, ACh, gastrin</td>
</tr>
<tr>
<td>Chief cells</td>
<td>Pepsinogen</td>
<td>Stimulated by vagal input and local acid</td>
</tr>
<tr>
<td>G-cells</td>
<td>Gastrin</td>
<td>Stimulates H⁺ production from parietal cells</td>
</tr>
<tr>
<td>Superficial epithelial cells</td>
<td>Mucus, HCO₃⁻</td>
<td>Protect gastric mucosa</td>
</tr>
<tr>
<td>Neuroendocrine cells</td>
<td>Multiple (e.g. somatostatin, inhibits cell secretion)</td>
<td>Involved in neural, hormonal, and paracrine pathways</td>
</tr>
</tbody>
</table>

Figure 5. Stimulation of H⁺ secretion from the parietal cell

Gastritis

Definition
- defined histologically: inflammation of the stomach mucosa

Etiology
- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

Table 5. Updated Sydney Classification of Gastritis

<table>
<thead>
<tr>
<th>Type</th>
<th>Common Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Gastritis</td>
<td>Alcohol⁹, Aspirin⁹/NSAID⁹, shock/physiological stress* (seen in ICU patients)</td>
</tr>
<tr>
<td>Hemorrhagic/erosive gastritis</td>
<td>H. pylori*</td>
</tr>
<tr>
<td>Helicobacter gastritis</td>
<td></td>
</tr>
<tr>
<td>Chronic Gastritis</td>
<td></td>
</tr>
<tr>
<td>Non-atrophic</td>
<td>H. pylori*</td>
</tr>
<tr>
<td>Atrophic</td>
<td>H. pylori*, dietary, environmental factors (multi-focal), autoimmunity</td>
</tr>
<tr>
<td>Chemical</td>
<td>NSAID⁹*, bile</td>
</tr>
<tr>
<td>Radiation</td>
<td>Radiation injury</td>
</tr>
<tr>
<td>Lymphocytic</td>
<td>Celiac disease, drug</td>
</tr>
<tr>
<td>Eosinophilic</td>
<td>Food allergies</td>
</tr>
<tr>
<td>Non-infectious granulomatous</td>
<td>Crohn’s disease, sarcoidosis</td>
</tr>
<tr>
<td>Other infectious gastritides</td>
<td>Bacteria, viruses, fungi, parasite, TB, syphilis</td>
</tr>
</tbody>
</table>

*Most common causes
Clinical Features
- non-erosive gastritis is asymptomatic (except in certain rare causes like Crohn’s disease); difficult to diagnose clinically or endoscopically
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

Management
- determined by etiology (see \textit{H. pylori}, G13, NSAID, G14 and \textit{Stress-Induced Ulceration}, G14)
- non-pharmacological: avoidance of mucosal irritants such as alcohol, NSAIDs, and foods that trigger symptoms

### Peptic Ulcer Disease

#### Definition
- focal defects in the mucosal that penetrate the muscularis mucosal layer results in scarring (defects superficial to the muscularis mucosa have erosions and no scarring)
- peptic ulcer disease includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

#### Etiology

<table>
<thead>
<tr>
<th></th>
<th>Duodenal</th>
<th>Gastric</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{H. pylori} infection</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>Physiologic stress-induced</td>
<td>&lt;3%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Zollinger-Ellison (ZE) syndrome</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- NSAID negative, \textit{H. pylori} negative ulcers becoming more commonly recognized
- others: CMV, ischemic, idiopathic
- alcohol: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with tobacco, cirrhosis of liver, COPD, and chronic renal failure

#### Clinical Features
- dyspepsia: most common presenting symptom
  - only 20% of patients with dyspepsia have ulcers, while most have functional disease
  - may present with complications
    - bleeding 10% (severe if from gastroduodenal artery) (see \textit{Bleeding Peptic Ulcer}, G13)
    - perforation 2% (usually anterior ulcers)
    - gastric outlet obstruction 2%  
    - penetration (posterior) 2%; may also cause pancreatitis
- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters over wk with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

#### Investigations
- endoscopy (most accurate)
- upper GI series
- \textit{H. pylori} tests (see Table 7)
- fasting serum gastrin measurement if Zollinger-Ellison (ZE) syndrome suspected

#### Treatment
- specific management depends on etiology (see \textit{H. pylori}, G13, NSAID, G14 and \textit{Stress-Induced Ulceration}, G14)
- eradicate \textit{H. pylori} if present, chief advantage is to lower ulcer recurrence rate
- stop NSAIDs if possible
- start PPI: inhibits parietal cell H⁺/K⁺-ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other meds (e.g. histamine H₂-antagonists) less effective
- discontinue tobacco
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol, and spices

### Approach to PUD
- Stop NSAIDs
- Acid neutralization
- \textit{H. pylori} eradication
- Quit smoking

### Cigarette Smoking and PUD
- Increased risk of ulcer
- Increased risk of complications
- Increased chance of death from ulcer
- Impairs healing

### Bleeding Peptic Ulcers: Risk Factors for Increased Mortality
- Co-existent illness
- Hemodynamic instability
- Age >60 yr
- Transfusion required
**Management of Bleeding Peptic Ulcers**

- OGD to explore upper GI tract
- establish risk of rebleeding/continuous bleed
  - clinical risk factors: increased age (>60), bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
  - if high risk, consider ICU admission

**Suspected Bleeding Peptic Ulcer**

<table>
<thead>
<tr>
<th>ABCs: assess vitals (BP and HR, orthostatic changes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC, lymes, BUN, Cr, INR, blood type, cross and type</td>
</tr>
<tr>
<td>Resuscitate: crystalloids and blood products if indicated</td>
</tr>
</tbody>
</table>

**Endoscopy**

- Active bleeding or visible vessel
  - High Risk: Hemostasis: clips, thermal coagulation ± epinephrine injection
  - Continue (or start) IV PPI
  - Monitor for re-bleeding in hospital
  - If adherent clot: consider removal

- Flat, pigmented spot or clean base
  - Low Risk: No hemostasis necessary
  - Continue (or start) oral PPI
  - Decreased need for in-hospital monitoring

**Post-Endoscopy**

- Resume clear fluids 6 hours post-endoscopy
- Test for H. pylori
- Counsel re: most likely causes (NSAIDs, anti-platelet agents)
- If re-bleeding: repeat endoscopy with aim of hemostasis
- Consult interventional radiology or surgery if needed

**Figure 6. Approach to management of suspected bleeding peptic ulcer**

Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937

**H. pylori-Induced Peptic Ulceration**

**Pathophysiology**

- *H. pylori*: Gram-negative flagellated rod that resides on but does not invade the gastric mucosa
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- mucosal defenses moderated by PGE2 and blood flow, mucus, etc.
- theories of how *H. pylori* causes ulcers: none satisfactory, but pattern of colonization correlates with outcome
  - gastritis only in antrum (15% of patients), high gastric acid, associated with peptic ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
  - gastritis throughout stomach (“pangastritis” – 85% of patients), low gastric acid, associated with cancer

**Epidemiology**

- *H. pylori* is found in about 30-40% of all Americans, with rates higher in African-American and Hispanic populations
  - highest prevalence in those raised during 1930s
  - infection most commonly acquired in childhood, presumably by fecal-oral route
  - high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

**Outcome**

- gastritis (non-erosive) in 100% of patients but asymptomatic
- peptic ulcer in 15% of patients
- gastric malignancy (gastric carcinoma and mucosal associated lymphomatous tissue [MALT] lymphoma in 0.5% of patients)
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/gastric malignancy and prevent spread to others (mostly children <5 yr of age)

**Intragastric pH with Oral vs. Intravenous Bolus plus Infusion Proton-pump Inhibitor Therapy in Patients with Bleeding Ulcers**

Gastroenterology 2008;134:1836-1841

**Study:** Randomized control trial.

**Participants:** Patients presenting with overt bleeding from an ulcer.

**Intervention:** Patients received either IV lansoprazole (90 mg bolus followed by 9 mg/h infusion; n=32) or oral lansoprazole (120 mg bolus followed by 30 mg every 3 h; n=34).

**Primary Outcome:** 24 h pH.

**Results:** Intragastric pH was >6 for >60% of the study period in 22 (68.8%) patients receiving IV and 22 (64.7%) patients receiving oral PPI. At 1 h, mean pHs for IV and oral were 5.3 and 3.3, respectively (difference 2.0; p=0.001). After 1.5 h, there were no differences in mean pH between the groups. Mean pH rose above 6 after 2.3 h of IV PPI and 3.4 h of oral PPI.

**Conclusion:** Frequent oral PPI may be able to replace the currently recommended IV bolus plus infusion PPI therapy in patients with bleeding ulcers. However, IV PPI has a more rapid increase in pH, reaching mean pH of 6 approximately 1 h sooner than oral PPI.
Investigations

Table 7. Diagnosis of *H. pylori* Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-invasive Tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea breath test</td>
<td>90-100%</td>
<td>89-100%</td>
<td>Affected by PPI therapy (false negatives)</td>
</tr>
<tr>
<td>Serology</td>
<td>88-99%</td>
<td>89-95%</td>
<td>Can remain positive after treatment</td>
</tr>
<tr>
<td>Stool antigen test</td>
<td>95-97%</td>
<td>94-98%</td>
<td>Useful for diagnosing acute infection</td>
</tr>
<tr>
<td><strong>Invasive Tests (require endoscopy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>93-99%</td>
<td>95-99%</td>
<td>Gold standard; affected by PPI therapy (false negatives)</td>
</tr>
<tr>
<td>Rapid urease test (on biopsy)</td>
<td>89-98%</td>
<td>93-100%</td>
<td>Rapid</td>
</tr>
<tr>
<td>Microbiology culture</td>
<td>98%</td>
<td>95-100%</td>
<td>Research only</td>
</tr>
</tbody>
</table>

**Treatment: *H. pylori* Eradication**
- triple therapy for 7-14 d (Hp-Pac®): PPI bid (e.g. lansoprazole 30 mg bid) + amoxicillin 1 g bid + clarithromycin 500 mg bid
  - 80% success rate
- quadruple therapy for 10-14 d: PPI bid + bismuth 525 mg qid + tetracycline 500 mg qid + metronidazole 250 mg qid
  - only recommended as first line therapy if resistance to clarithromycin or metronidazole is high, or in patients with recent or repeated exposure to these drugs
  - levofloxacin can replace metronidazole or tetracycline
- sequential therapy
  - days 1-5: PPI bid + amoxicillin 1 g bid
  - days 6-10: PPI bid + clarithromycin 500 mg bid + tinidazole 500 mg bid
- 5-15% of cases are resistant to all known therapies

**NSAID-Induced Ulceration**
- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
  - erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically silent: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

**Pathophysiology**
- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (intravenous NSAID causes ulcers, but not erosions), inhibits mucosal cyclooxygenase, leading to decreased synthesis of protective prostaglandins, thus leading to ulcers

**Risk Factors For NSAID Causing Peptic Ulcer**
- previous peptic ulcers/UGIB
- age
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

**Treatment**
- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acemetaminophen
- combine NSAID with PPI or misoprostol
- enteric coating of Aspirin® (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration

**Stress-Induced Ulceration**

**Definition**
- ulceration or erosion in the upper GI tract of ill patients, usually in ICU
- lesions most commonly in fundus of stomach

**Pathophysiology**
- unclear: likely involves ischemia; may be caused by CNS disease, acid hypersecretion, Cushing ulcers
- physiological stress (e.g. fever, severe illness, complex post-operative course) causes ulcers and erosions
Risk Factors
• mechanical ventilation
• anti-coagulation
• multi-organ failure
• septicemia
• severe surgery/trauma
• CNS injury (“Cushing's ulcers”)
• burns involving more than 35% of body surface

Clinical Features
• UGIB (see Upper Gastrointestinal Bleeding, G25)
• painless

Treatment
• prophylaxis with gastric acid suppressants (H2-blockers or PPI) decreases risk of UGIB, but may increase risk of pneumonia
• treatment same as for bleeding peptic ulcer but often less successful

Gastric Carcinoma
• see General Surgery, GS18

Small and Large Bowel

Classification of Diarrhea

Definition
• clinically: diarrhea defined as stools that are looser and/or more frequent than normal;
  physiologically: 24 h stool weight >200 g (less useful clinically)

Classification
• acute vs. chronic
• small volume (tablespoons of stool; typical of colonic diseases) vs. large volume
  (>1/2 cup stool; typical of small bowel diseases)
• watery (bowel disease) vs. steatorrhea
• secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)

Acute Diarrhea

Definition
• passage of frequent unformed stools for <14 d

Etiology
• most commonly due to infections
• most infections are self-limiting and resolve within 7 d

Risk Factors
• food (seafood, chicken, turkey, eggs, beef)
• medications: antibiotics, laxatives
• others: high risk sexual activity, infectious outbreaks, family history (IBD)

Classification
• broadly divided and classified into inflammatory and non-inflammatory diarrhea
• mechanisms
  ▪ stimulation of intestinal water secretion and inhibition of water absorption (i.e. secretory problem)
  ▪ in inflammatory diarrhea, organisms and cytotoxins invade mucosa, killing mucosal cells and further perpetuating the diarrhea

Table 8. Classification of Acute Diarrhea

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Disruption of intestinal mucosa</td>
</tr>
<tr>
<td>Site</td>
<td>Usually colon</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>Usually abnormal mucosa seen</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Bloody (not always) Small volume, high frequency Often lower abdominal cramping with urgency ± tenesmus May have fever ± shock</td>
</tr>
<tr>
<td>Investigations</td>
<td>Fecal WBC and RBC positive</td>
</tr>
</tbody>
</table>
Table 8. Classification of Acute Diarrhea (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differential Diagnosis</td>
<td>Acute presentation of idiopathic inflammatory bowel disease</td>
<td>Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease)</td>
</tr>
<tr>
<td>Significance</td>
<td>Higher yield with stool C&amp;S</td>
<td>Lower yield with stool C&amp;S</td>
</tr>
<tr>
<td></td>
<td>Can progress to life-threatening megacolon, perforation, hemorrhage</td>
<td>Chief life-threatening problem is electrolyte disturbances/ fluid depletion</td>
</tr>
<tr>
<td>Antibiotics may benefit</td>
<td></td>
<td>Antibiotics unlikely to be helpful</td>
</tr>
</tbody>
</table>

Investigations
- stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (day care worker, nursing home resident, community outbreaks (e.g. Walkerton), etc.)
  - C&S only tests Campylobacter, Salmonella, Shigella, E. coli
  - other organisms must be ordered separately
- flexible sigmoidoscopy: useful if inflammatory diarrhea suspected
- biopsies are the most useful method of distinguishing idiopathic IBD (Crohn’s disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- C. difficile toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home, or recent chemotherapy

Treatment
- fluid and electrolyte replacement orally in most cases, intravenous if severe extremes of age/coma
- anti-diarrheals
  - antimitoty agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
  - side effects: abdominal cramps, toxic megacolon
  - absorbants: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
    - act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
  - much less effective than antimitoty agents
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful
- antibiotics: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially Salmonella)
    - drug side effects (including C. difficile infection)
    - development of resistant strains
    - renal failure/hemolysis (enterohemorrhagic E. coli O157:H7)
  - indications for antimicrobial agents in acute diarrhea
    - sepsis
    - prolonged fever with fecal blood or leukocytes
    - clearly indicated: Shigella, V. cholerae, C. difficile, traveler’s diarrhea (enterotoxigenic E. coli [ETEC]), Giardia, Entamoeba histolytica, Cyclospora
    - much less effective than antimitoty agents
- antimicrobial agents indicate: Salmonella, Campylobacter, Yersinia, non-enterotoxigenic E. coli
- Salmonella: always treat Salmonella typhi (typhoid or enteric fever); treat other Salmonella only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneuryms, prosthetic valve grafts/joints, sickle cell disease

Traveler’s Diarrhea
- see Infectious Diseases, ID14

Chronic Diarrhea

Definition
- passage of frequent unformed stool for >14 d
- approach is similar to that of acute diarrhea except that the majority of cases are non-infectious

Etiology/Classification
- see Differential Diagnosis of Common Presenting Complaints, G4

Investigations
- guided by history
- stool analysis for: C. difficile toxin, C&S, O&P ± fecal fat, WBC
- blood for: CBC, electrolytes, CRP, TSH, celiac serology (IgA anti-tTG; ask for serum protein electrophoresis or immunoglobulin quantitation to rule out IgA deficiency which has an increased frequency in celiac disease)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (low yield)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease
Maldigestion and Malabsorption

**Definition**
- *maldigestion*: inability to break down large molecules in the lumen of the intestine into their component small molecules
- *malabsorption*: inability to transport molecules across the intestinal mucosa into circulation
- *malassimilation*: encompasses both maldigestion and malabsorption

**Etiology**
- *maldigestion*
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis, cancer)
  - bile salt deficiency
    - terminal ileal disease (impair recycling), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic)
  - specific enzyme deficiencies (e.g. lactase)
- *malabsorption*
  - inadequate absorptive surface
  - infections/infestations (e.g. Whipple’s disease, Giardia)
  - immunologic or allergic injury (e.g. celiac disease)
  - infiltration (e.g. lymphoma, amyloidosis)
  - fibrosis (e.g. systemic sclerosis, radiation enteritis)
  - bowel resection (length, site, and location are important)
  - extensive Crohn's disease
  - drug-induced
    - cholestyramine, ethanol, neomycin, tetracycline, and other antibiotics
  - endocrine
    - DM (complex pathogenesis)

**Clinical Features**
- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency

**Table 9. Absorption of Nutrients and Fat Soluble Vitamins**

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Absorption</th>
<th>Clinical Disease and/or Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Duodenum, upper jejunum</td>
<td>Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails), pica</td>
<td>↓ Hb, ↓ serum Fe, ↓ serum ferritin</td>
</tr>
<tr>
<td>Calcium</td>
<td>Duodenum, upper jejunum (binds to Ca⁺⁺ binding-protein in cells; levels increased by Vit D)</td>
<td>Metabolic bone disease, may get tetany and pancreatitis if serum calcium falls (see Endocrinology, E40)</td>
<td>↓ serum Ca⁺⁺, ↓ serum Mg²⁺, and ↑ ALP Evaluate for ↓ bone mineralization radiographically (DEXA)</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Jejunum</td>
<td>Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)</td>
<td>↓ serum folic acid</td>
</tr>
<tr>
<td>Vitamin B₁₂</td>
<td>B₁₂ ingested and bound to R proteins mainly from salivary glands; stomach secretes intrinsic factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B₁₂-IF complex forms, protecting B₁₂ from further protease attack; B₁₂ absorbed in ileum and binds to transcobalamin (TC)</td>
<td>Subacute combined degeneration of the spinal cord, peripheral/optic neuropathy, dementia, megaloblastic anemia, glossitis</td>
<td>Differentiate causes by nuclear Schilling test (when available) Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H24)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Complex polysaccharides hydrolyzed to oligosaccharides and disaccharides by salivary and pancreatic enzymes</td>
<td>Generalized malnutrition, weight loss, flatuln, and diarrhea</td>
<td>Hydrogen breath test Trial of carbohydrate-restricted diet D-xylose test</td>
</tr>
<tr>
<td>Protein</td>
<td>Digestion at stomach, brush border, and inside cell Absorption occurs primarily in the jejunum</td>
<td>Generalized malnutrition and weight loss, anemia, and ↓ albumin if severe</td>
<td>↓ serum albumin (low sensitivity)</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipase, colipase, phospholipase A (pancreatic enzymes), and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat, and aid in absorption Fatty acids diffuse into cell cytoplasm</td>
<td>Generalized malnutrition, weight loss, and diarrhea Foul-smelling feces + gas Steatorrhea</td>
<td>Small bowel biopsy MRCP, ERCP, pancreatic function tests Quantitative stool fat test (72 h) May start with qualitative stool fat test (Sudan stain of stool) (C-troïk breath test)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)</td>
<td>Night blindness Dry skin Keratomalacia</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)</td>
<td>Osteomalacia in adults Rickets in children</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)</td>
<td>Retinopathy, neurological problems</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Synthesized by intestinal flora ↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation</td>
<td>Prolonged INR causes bleeding</td>
<td></td>
</tr>
</tbody>
</table>

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone.
**Investigations**

- transglutaminase serology/protein electrophoresis and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea (gold standard)
- serum carotene, folate, Ca\(^{2+}\), Mg\(^{2+}\), vitamin B\(_{12}\), albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear stained with Sudan (rarely used)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)
- trial of therapy with pancreatic enzymes

**Treatment**

- dependent on underlying etiology

---

### Celiac Disease (Gluten Enteropathy/Sprue)

**Definition**

- abnormal small intestine mucosa due to intestinal reaction to gliadin, a component of gluten found in cereal grains

**Etiology**

- only autoimmune disease in which antigen (a peptide in α-gliadin) is recognized
- associated with other autoimmune diseases, especially thyroid disease
- gluten, a protein in cereal grains, broken down to gliadin, is toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; also associated with HLA-DQ8

**Epidemiology**

- more common in women
- family history: 15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy

**Clinical Features**

- classically: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; now more commonly bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
  - thus iron, calcium, and folic acid deficiency more common than vitamin B\(_{12}\) deficiency
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

**Investigations**

- small bowel mucosal biopsy (usually duodenum) is diagnostic with:
  - villous atrophy and crypt hyperplasia
  - increased number of plasma cells and lymphocytes in lamina propria
  - increased intraepithelial lymphocytes
  - villous atrophy also seen in small bowel overgrowth, Crohn's, lymphoma, *Giardia*, HIV
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, Ca\(^{2+}\), Fe, albumin, cholesterol, carotene, B\(_{12}\) absorption
- improvement with a gluten-free diet; should not be started before anti-tTG and biopsy
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - IgA deficient patients have false-negative anti-tTG
  - thus measure serum IgA concomitantly (via serum protein electrophoresis)
- fecal fat >7%

**Treatment**

- dietary counseling
  - gluten free diet: avoid barley, rye, wheat
  - oats allowed if not contaminated by other grains
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
- if poor response to diet change, consider
  - alternate diagnosis
  - non-adherence to gluten-free diet
  - concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
- development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain, weight loss, palpable mass)
- development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell population (precursor to lymphoma)

**Prognosis**
- associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon)
- risk of malignancy may be lowered by dietary gluten restriction

## Inflammatory Bowel Disease

### Definition
- Crohn's disease (CD), ulcerative colitis (UC), indeterminate colitis or IBD-unclassified (IBDU)

### Pathophysiology
- poorly understood
- sustained response of the immune system, perhaps to enteric flora in a genetically predisposed individual
- current hypothesis: lack of appropriate down-regulation of immune responsiveness

### Genetics
- increased risk of both UC and CD in relatives of patients with either disease, especially siblings, early onset disease
- familial risk greater if proband has CD rather than UC
- likely polygenomic pattern: 9 gene loci are associated
- CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in homozygote is 40), especially Ashkenazi Jews, early onset disease, ileal involvement, fistulizing and stenotic disease
- CARD15 gene product modulates NFκB, which is required for the innate immune response to microbial pathogens, best expressed in monocytes-macrophages

### Clinical Features

**Table 10. Clinical Differentiation of Ulcerative Colitis from Crohn’s Disease**

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Any part of GI tract</td>
<td>Isolated to large bowel</td>
</tr>
<tr>
<td></td>
<td>• Small bowel + colon: 50%</td>
<td>Always involves rectum, may progress proximally</td>
</tr>
<tr>
<td></td>
<td>• Small bowel only: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Colon only: 20%</td>
<td></td>
</tr>
<tr>
<td><strong>Rectal Bleeding</strong></td>
<td>Uncommon</td>
<td>Very common (90%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Less prevalent</td>
<td>Frequent small stools</td>
</tr>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>Post-prandial/colickey</td>
<td>Less common</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Urgency/Tenesmus</strong></td>
<td>Uncommon (unless rectum involved)</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Palpable Mass</strong></td>
<td>Frequent (25%, RLQ)</td>
<td>Rare (if present, cecum full of stool)</td>
</tr>
<tr>
<td><strong>Recurrence After Surgery</strong></td>
<td>Common</td>
<td>None post- colectomy</td>
</tr>
<tr>
<td><strong>Endoscopic Features</strong></td>
<td>Ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning</td>
<td>Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps</td>
</tr>
<tr>
<td><strong>Histologic Features</strong></td>
<td>Transmural distribution with skip lesions</td>
<td>Mucosal distribution, continuous disease (no skip lesions)</td>
</tr>
<tr>
<td></td>
<td>Fecal inflammation</td>
<td>Granulomas absent</td>
</tr>
<tr>
<td></td>
<td>± noncaseating granulomas, deep</td>
<td>Gland destruction, crypt abscess</td>
</tr>
<tr>
<td></td>
<td>fissuring + aphthous ulcerations, strictures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glands intact</td>
<td></td>
</tr>
<tr>
<td><strong>Radiologic Features</strong></td>
<td>Cobblestone mucosa</td>
<td>Lack of haustera</td>
</tr>
<tr>
<td></td>
<td>Frequent strictures and fistulae AXR: bowel wall thickening &quot;string sign&quot;</td>
<td>Strictures rare; need to rule out complicating cancer</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Strictures, fistulae, perianal disease</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td><strong>Colon Cancer Risk</strong></td>
<td>Increased if &gt; 30% of colon involved</td>
<td>Increased except in proctitis</td>
</tr>
</tbody>
</table>
Table 11. Extraintestinal Manifestations (EIM) of IBD

<table>
<thead>
<tr>
<th>System</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>10%</td>
<td>Less common</td>
</tr>
<tr>
<td>Perianal skin tags</td>
<td>75-80%</td>
<td>Rare</td>
</tr>
<tr>
<td>Oral mucosal lesions</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Common</td>
<td>15-20% of those with IBD (CD &gt; UC)</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>15-20%</td>
<td>10% of those with IBD (CD &gt; UC)</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>15-20% of those with IBD (CD &gt; UC)</td>
<td>Occurs equally in CD and UC</td>
</tr>
<tr>
<td>Ocular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis (vision threatening)</td>
<td>3-4% of IBD patients (CD &gt; UC)</td>
<td></td>
</tr>
<tr>
<td>Episcleritis (benign)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>15-35% of patients with ileal Crohn’s</td>
<td></td>
</tr>
<tr>
<td>PSC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatty liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculi</td>
<td>Most common in CD, especially following ileal resection</td>
<td></td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistulae</td>
<td>Characteristic of Crohn’s</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin deficiencies (B12, Vit ADEK)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis (rare)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Crohn’s Disease

Definition
- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region (“gum to bum”)

Epidemiology
- incidence 1-6/100,000; prevalence 10-100/100,000
- bimodal: onset before 30 yr, second smaller peak age 60; M=F
- incidence of Crohn’s increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in Crohn’s patients is higher than general population

Pathology
- most common location: ileum + ascending colon
- linear ulcers leading to mucosal islands and “cobblestone” appearance
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

Clinical Features
- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- most often presents as recurrent episodes of abdominal cramps, diarrhea, and weight loss
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- extra-intestinal manifestations are more common with colonic involvement
- fistulae, fissures, abscesses are common
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina, and other parts of bowel

Investigations
- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response
- bacterial cultures, O&P, C. difficile toxin to exclude other causes of inflammatory diarrhea

Figure 7. Traditional graded approach to induction therapy in Crohn’s disease

Note: Starting with immunosuppressives plus immunomodulators (“bottom-up approach”) increasingly being used (Lancet 2008;371:660-667). Combination of azathioprine and infliximab has the highest remission rate yet described with medical treatment (NEJM 2010;362:1383-1395).
Management (see Figure 7)

Table 12. Management of Crohn’s Disease

<table>
<thead>
<tr>
<th>Management</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle/Diet</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td></td>
<td>Fluids only during acute exacerbation</td>
</tr>
<tr>
<td></td>
<td>Enteral diets may aid in remission</td>
</tr>
<tr>
<td></td>
<td>No evidence for any non-enteral diet changing the natural history of Crohn’s disease, but may affect symptoms</td>
</tr>
<tr>
<td></td>
<td>Those with extensive small bowel involvement or extensive resection require electrolyte, mineral, and vitamin supplements (vit D, Ca²⁺, Mg²⁺, zinc, Fe, B₁₂)</td>
</tr>
<tr>
<td>Antidiarrheal Agents*</td>
<td>Loperamide (Imodium®) &gt; diphenoxylate (Lomotil®) &gt; codeine (cheap but addictive)</td>
</tr>
<tr>
<td></td>
<td>All work by decreasing small bowel motility</td>
</tr>
<tr>
<td></td>
<td>CAUTION if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups</td>
</tr>
<tr>
<td>5-ASA</td>
<td>Efficacy controversial: most evidence for mild colonic disease</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine</td>
</tr>
<tr>
<td></td>
<td>Hydrolysis by intestinal bacteria releases 5-ASA (active component)</td>
</tr>
<tr>
<td></td>
<td>Dose-dependent efficacy</td>
</tr>
<tr>
<td></td>
<td>Mesalamine (Pentasa®): coated 5-ASA releases 5-ASA in the ileum and colon</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>e.g. metronidazole (20 mg/kg/d, bid or tid dosing) or ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Best described for perianal Crohn’s, although characteristically relapse when discontinued</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone: starting dose 40 mg OD for acute exacerbations; IV methylprednisolone if severe</td>
</tr>
<tr>
<td></td>
<td>No proven role for steroids in maintaining remissions; masks intra-abdominal sepsis</td>
</tr>
<tr>
<td>Immunosuppressives</td>
<td>6-mercaptopurine (6-MP), azathioprine (Imuran®); methotrexate (used less often)</td>
</tr>
<tr>
<td></td>
<td>More often used to maintain remission than to treat active inflammation</td>
</tr>
<tr>
<td></td>
<td>Most commonly used as steroid-sparing agents</td>
</tr>
<tr>
<td></td>
<td>i.e. to lower risk of relapse as corticosteroids are withdrawn</td>
</tr>
<tr>
<td></td>
<td>May require ≥3 mo to have beneficial effect; usually continued for several years</td>
</tr>
<tr>
<td></td>
<td>May help to heal fistulae, decrease disease activity</td>
</tr>
<tr>
<td></td>
<td>Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy</td>
</tr>
<tr>
<td>Biologics</td>
<td>Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α</td>
</tr>
<tr>
<td></td>
<td>Proven effective for treatment of fistulae and patients with medically refractory CD</td>
</tr>
<tr>
<td></td>
<td>First-line immunosuppressive therapy with infliximab + azathioprine more effective than using either alone</td>
</tr>
<tr>
<td>Surgical/Experimental</td>
<td>Surgical treatment (see General Surgery, GS30)</td>
</tr>
<tr>
<td></td>
<td>Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding, and for medically refractory disease</td>
</tr>
<tr>
<td></td>
<td>If &lt;50% or &lt;200 cm of functional small intestine, risk of short bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>At least 50% clinical recurrence within 5 yr; 85%-within 15 yr; endoscopic recurrence rate even higher</td>
</tr>
<tr>
<td></td>
<td>40% likelihood of second bowel resection, 30% likelihood of third bowel resection</td>
</tr>
<tr>
<td></td>
<td>Complications of ileal resection:</td>
</tr>
<tr>
<td></td>
<td>&lt;100 cm resected → watery diarrhea or cholorrhea (impair bile salt absorption)</td>
</tr>
<tr>
<td></td>
<td>Treatment: cholestyramine or anti-diarrheals e.g. loperamide</td>
</tr>
<tr>
<td></td>
<td>&gt;100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency)</td>
</tr>
<tr>
<td></td>
<td>Treatment: fat restriction, medium chain triglycerides</td>
</tr>
</tbody>
</table>

*Cholestyramine: a bile-salt binding resin; for watery diarrhea with <100 cm of terminal ileum diseased or resected; however, non-specific anti-diarrheals are more convenient and often more potent.

Prognosis

- highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- complications include:
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as ulcerative colitis (see Ulcerative Colitis, G22) if more than 1/3 of colon involved

Traditional Medical Management of Crohn’s

<table>
<thead>
<tr>
<th>Induction of Remission</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>?</td>
</tr>
<tr>
<td>Steroids</td>
<td>+</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>+</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>+</td>
</tr>
<tr>
<td>MTX</td>
<td>+</td>
</tr>
<tr>
<td>Infliximab</td>
<td>+</td>
</tr>
</tbody>
</table>

Biological Therapies for Inflammatory Bowel Diseases

- Anti-TNF Agents: infliximab, adalimumab, certolizumab: Effective in CD, less effective for UC. Increase mucosal healing, decrease need for hospitalizations and surgeries, and can induce steroid-free remission. At least 10% of patients annually develop intolerance and/or a loss of response.
- Selective Anti-Adhesion Molecules
  - Infliximab: Increases response and remission rates, circulating leukocytes, and steroid-sparing capacity in CD. Progressive multifocal leukoencephalopathy is a rare adverse event.
- Promising New BT: Anti-Interleukin-12
  - Interleukin-23 p40 target factors more often associated with CD, while anti-IFN-α antibodies may treat CD and UC.
- BT Without Established Efficacy: Recombinant human cytokines, blockade of T-cell activation (fotolizumab and basiliximab) and stimulators of the innate immune system.

Conclusion: Anti-TNF agents are effective treatments for IBD. There is a need to develop salvage biological therapies for patients who do not respond to a first biological drug. BT’s have a safety risk, so their place in treatment algorithms must be defined carefully.

Characteristic more than 1 yr between onset of symptoms and diagnosis of Crohn’s disease
Ulcerative Colitis

Definition
- inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

Epidemiology
- incidence 2-10/100,000; prevalence 35-100/100,000 (more common than Crohn's)
- 2/3 onset by age 30 (with second peak after 50); M=F
- small hereditary contribution (15% of cases have 1st degree relative with disease)
- risk is less in smokers
- inflammation limited to rectum or left colon is more common than pancolitis

Pathology
- disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
- inflammation is diffuse, continuous and confined to mucosa

Clinical Features
- rectal bleeding is the hallmark feature, however diarrhea may be present if more than the rectum is involved
  ▪ can also have abdominal cramps/pain, especially with defecation
- severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
- tenesmus, urgency, incontinence
- systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
- extra-intestinal manifestations (see Table 11)
- characteristic exacerbations and remissions; 5% of cases are fulminant

Investigations
- sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis
- colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
- CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease
- stool culture, microscopy, C. difficile toxin assay necessary to exclude infection
- no single confirmatory test

Management
- mainstays of treatment: 5-ASA (mesalamine) derivatives and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
- diet of little value in decreasing inflammation but may alleviate symptoms
- antidiarrheal medications generally not indicated in UC
- 5-ASA
  ▪ topical (suppository or enema): very effective for distal disease (distal to splenic flexure), preferable to corticosteroids
  ▪ oral: effective for mild to moderate, but not severe colitis (4 g/d)
  ▪ e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d
  ▪ commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
  ▪ may decrease rate of colorectal cancer
- corticosteroids
  ▪ to remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h)
  ▪ limited role as maintenance therapy
  ▪ use suppositories for proctitis, enemas for proctosigmoiditis
  ▪ topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
- immunosuppressants (steroid-sparing)
  ▪ if severe UC is refractory to steroid therapy, consider adding IV cyclosporine or IV infliximab within 3-5 d of recognition of need for salvage – rapidly effective, but helpful only in a minority of patients
  ▪ azathioprine: too slow to rapidly resolve acute relapse
  ▪ most commonly used to induce and maintain remission as corticosteroids withdrawn
- surgical treatment
  ▪ early in severe UC, especially fulminant cases and toxic megacolon – consider operation if no response after 3-5 d of corticosteroids, or after 4-7 d of immunosuppressive medical therapy
  ▪ aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastomosis (IPAA)
  ▪ indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids, overt malignancy

In UC, non-bloody diarrhea is frequently the initial presentation; eventually progressing to bloody diarrhea
Complications
- similar to CD, except
  - more liver problems (especially PSC in men)
  - greater risk of colorectal cancer
    - risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%)
    - risk also increases with active mucosal inflammation and sclerosing cholangitis
    - thus, regular colonoscopy and biopsy in pancolitis of ≥8 yr is indicated
  - toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery, GS26)

Prognosis
- chronic relapsing pattern in most patients
- 10-15% chronic continuous pattern
- >1 attack in almost all patients
- more colonic involvement in the 1st yr correlates with increased severity of attacks and increased colectomy rate
  - colectomy rate = 1% for all patients after the 1st yr; 20-25% eventually undergo colectomy
- normal life expectancy
- if proctitis only, usually benign course

Irritable Bowel Syndrome

Definition
- a form of functional bowel disease, more than just a label for GI symptoms unexplained after investigations

Epidemiology
- 20% of North Americans
- onset of symptoms usually in young adulthood
- F>M
**Pathophysiology**

- associated with either abnormal perception of intestinal activity or abnormal intestinal motility
- abnormal motility: multiple abnormalities described; unclear if associations or if causative
- psychological: stress may increase IBS symptoms but does not cause IBS

**Diagnosis**

**Table 13. Rome III Criteria for Diagnosing Irritable Bowel Syndrome**

<table>
<thead>
<tr>
<th>IBS Rome III Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥12 wk in the past 12 mo of abdominal discomfort or pain that has 2 out of 3 features:</td>
</tr>
<tr>
<td>• Relieved with defecation</td>
</tr>
<tr>
<td>• Associated with a change in frequency of stool</td>
</tr>
<tr>
<td>• Associated with a change in consistency of stool</td>
</tr>
<tr>
<td>• The following are supportive, but not essential to the diagnosis:</td>
</tr>
<tr>
<td>• Abnormal stool frequency (&gt;3/d or &lt;3/wk)</td>
</tr>
<tr>
<td>• Abnormal stool form (lumpy/hard/loose/watery) &gt;1/4 of defecations</td>
</tr>
<tr>
<td>• Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) &gt;1/4 of defecations</td>
</tr>
<tr>
<td>• Passage of mucus &gt;1/4 of defecations</td>
</tr>
<tr>
<td>• Bloating</td>
</tr>
</tbody>
</table>

**Diagnosis of IBS Less Likely in Presence of “Red Flag” Features**

| Weight loss | Anemia |
| Fever | Blood or pus in stool |
| Nighturnal defecation | Abnormal gross findings on flexible sigmoidoscopy |

**Investigations**

- if history consistent with Rome III criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
- aim is to rule out diseases which mimic IBS
- CBC, TSH, albumin, CRP, tTG serology with protein electrophoresis
- stool for C&S, O&P, fecal fat if diarrhea present
- consider sigmoidoscopy

**Management**

- reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction
- no therapeutic agent consistently effective, pain most difficult to control
- symptom-guided treatment
  - pain predominant
    - antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine)
    - increase dietary fiber (bran or psyllium)
  - diarrhoea predominant (IBS-D)
    - increase dietary fiber (bran or psyllium) to increase stool consistency
    - loperamide (Imodium*)
    - diphenoxylate (Lomotil*)
  - constipation predominant (IBS-C)
    - exercise and increase fiber in diet
    - osmotic or other laxatives
  - mixed (alternating constipation and diarrhea) (IBS-M)

**Prognosis**

- 80% improve over time
- most have intermittent episodes
- normal life expectancy

**Constipation**

**Definition**

- passage of infrequent or hard stools with straining (stool water <50 mL/d); bowel frequency <3 times/wk

**Epidemiology**

- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries
Etiology
• If constipation is the only presenting symptom, underlying disease is only rarely found. Only test indicated in this situation is a complete blood count (2013 recommendation of American Gastroenterology Association), but consider TSH, calcium, and glucose
• Most common: idiopathic attributed to colon dysmotility but this is difficult to measure
• Organic causes
  • Medication side effects (narcotics, antidepressants) are the most common
  • Intestinal obstruction, left sided colon cancer (consider in older patients), and fecal impaction
  • Metabolic
    • DM
    • Hypothyroidism
    • Hypercalcemia, hypokalemia, uremia
  • Neurological
    • Intestinal pseudo-obstruction
    • Parkinson’s disease
    • MS
    • Collagen vascular disease (e.g. scleroderma)
    • Painful anal conditions (e.g. fissures)

Clinical Presentation
• Overlaps with irritable bowel syndrome
• Stool firm, difficult to expel, passed with straining, abdominal pain relieved by defecation, flatulence, overflow diarrhea, tenesmus, abdominal distension, infrequent BMs (<3/wk)

Investigations
• Colon visualization if concomitant symptoms such as rectal bleeding, weight loss, or anemia (colonoscopy, CT colonography)
• If refractory to treatment, consider classification based on colon transit time; can measure colon transit time with radioopaque markers that are ingested and followed with a series of plain film abdominal x-rays (normal: 70 h)
  1. Normal = misperception of normal defecation (IBS)
  2. Prolonged throughout = “colonic inertia” (infrequent bowel movements with gas/bloating, tends to occur in youth)
  3. Outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
• Combination of (2) and (3) common

Treatment (in order of increasing potency)
• Dietary fiber
  • Useful if mild or moderate constipation, but not if severe
  • Aim for 30 g daily, increase dose slowly
• Surface-acting (soften and lubricate)
  • Docusate salts, mineral oils
• Osmotic agents (effective in 2-3 d)
  • Lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, i.e. milk of magnesia), lactitol, polyethylene glycol 3350
• Cathartics/stimulants (effective in 24 h)
  • Castor oil, senna (avoid prolonged use to prevent melanosis coli), bisacodyl
• Enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl suppository)
• Prokinetic agents (prucalopride)

Upper Gastrointestinal Bleeding

Definition
• Bleeding proximal to the ligament of Treitz (75% of GI bleeds)
  • Ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

Etiology
• Above the GE junction
  • Epistaxis
  • Esophageal varices (10-30%)
  • Esophagitis
  • Esophageal cancer
  • Mallory-Weiss tear (10%)
• Stomach
  • Gastric ulcer (20%) (see Peptic Ulcer Disease, G12)
  • Gastritis (e.g. from alcohol or post-surgery) (20%)
  • Gastric cancer
  • Gastric antral vascular ectasia (rare, associated with cirrhosis and CTD)
  • Dieulafoy’s lesion (very rare)
• duodenum
  • ulcer in bulb (25%)
  • aortoenteric fistula: usually only if previous aortic graft (see sidebar, G25)
  • coagulopathy (drugs, renal disease, liver disease)
  • vascular malformation (Dieulafoy’s lesion, AVM)

Clinical Features
• in order of decreasing severity of the bleed: hematochezia > hematemesis > coffee ground emesis > melena > occult blood in stool

Management (initial)
• stabilize patient (1-2 large bore IVs, IV fluids, monitor)
• send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
• keep NPO
• consider NG tube to determine upper vs. lower GI bleeding in some cases
• endoscopy (OGD): establish bleeding site + treat lesion
  • if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
• IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
• given to stabilize clot, not to accelerate ulcer healing
• if given before endoscopy, decreases need for endoscopic therapeutic intervention
• for variceal bleeds, octreotide 50 µg loading dose followed by constant infusion of 50 µg/h
• consider IV erythromycin (or metoclopramide) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach

Prognosis
• 80% stop spontaneously
• peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
• endoscopic predictors of rebleeding: spurt or ooze, visible vessel, fibrin clot
• can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no predictors of rebleeding
• H₂-antagonists have little impact on rebleeding rates and need for surgery
• esophageal varices have a high rebleeding rate (55%) and mortality (29%)

Approach to Iron Deficiency Anemia

![Image of Approach to Iron Deficiency Anemia]

- Overt GI bleeding (hematochezia, melena)
  - Yes: treat
  - No: wireless endoscopy capsule/double balloon endoscopy

- Source of bleeding found?
  - Yes: follow
  - No: proceed as if overt GI bleeding present

- Has the anemia resolved?
  - Yes: follow
  - No: proceed as if overt GI bleeding present

- Rule out non-GI sources of bleeding (e.g. menorrhagia, hemolytic anemia)

* Wireless endoscopy capsule results help double balloon endoscopy localize source of bleeding
* Angiography if overt bleeding hemodynamically significant, estimated >0.5 cc/min
* CT enterography if wireless endoscopy capsule/double balloon endoscopy not available

Figure 9. Approach to iron deficiency anemia

Esophageal Varices

Etiology
• almost always due to portal HTN
• often accompanied by varices in stomach

Clinical Features
• characteristically massive upper GI bleeding

Prognosis
• risk of bleeding: 30% in 1st yr
• risk of rebleeding: 50-70% (20% mortality at 6 wk)
In a prospective study of upper GI tract bleeding, mortality, recurrent bleeding, and adverse events were lower when transfusions were given only when the hemoglobin concentration fell below 7.0 g/dL, compared to transfusions given when the hemoglobin fell below 9.0 g/dL. The benefit was most marked in variceal bleeding with Child-Pugh Class A or B cirrhosis (see below under cirrhosis), but also seen in peptic ulcer. Exclusion criteria included exsanguinating bleeding, acute coronary syndrome, and stroke. N Engl J Med 2013;368:11-21.

**Mallory-Weiss Tear**

**Definition**
- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

**Etiology**
- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia usually present

**Clinical Features**
- hematemesis ± melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

**Management**
- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection ± clips or surgical repair

**Lower Gastrointestinal Bleeding**

**Definition**
- bleed distal to ligament of Treitz

**Etiology**
- if blood per rectum with hemodynamic instability, rule out upper GI source
- diverticular (60% from right colon)
- vascular
  - angiodysplasia
  - anorectal (hemorrhoids, fissures)
- neoplasm
  - cancer
  - polyps
- inflammation
  - colitis (ulcerative, infectious, radiation, ischemic)
  - post-polypectomy

**Clinical Features**
- hematochezia (see Figure 11)
- anemia
- occult blood in stool
- rarely melena

**Management**
- treat underlying cause
Figure 11. Approach to hematochezia

Colorectal Carcinoma
- see General Surgery, GS34

Colorectal Polyps
- see General Surgery, GS33

Familial Colon Cancer Syndromes
- see General Surgery, GS33

Benign Anorectal Disease
- see General Surgery, GS38

Liver

Investigations of Hepatobiliary Disease

A. TEST OF LIVER FUNCTION

Prothrombin Time (PT or INR)
- a marker of hepatic protein synthesis
- increased by
  - impaired hepatic protein synthesis (>80%) (including all coagulation factors except VIII) i.e. hepatocellular dysfunction
  - vitamin K deficiency
  - vitamin K administration promptly corrects PT in vitamin K deficiency (malnutrition, malabsorption, etc.) but not in hepatocellular dysfunction; thus in the absence of vitamin K deficiency, INR/PT is a reliable index of hepatocellular dysfunction

Serum Albumin Level
- a marker of hepatic protein synthesis; must exclude malnutrition, renal or GI losses, and significant inflammatory or malignant illness of any organ system

Serum Bilirubin
- marker of hepatic excretion; transport from hepatocyte to bile
- canaliculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect = unconjugated bilirubin
- liver dysfunction causes hyperbilirubinemia (elevated direct bilirubin) since conjugation preserved even in end stage liver failure

Serum transaminases >1000 due to
- Viral hepatitis
- Drugs
- Autoimmune hepatitis
- Hepatic ischemia
- Less often, common bile duct stone

ALT > AST = most causes of hepatitis
AST > ALT = alcoholic liver disease or other causes of hepatitis that have progressed to advanced cirrhosis

All clotting factors except factor VIII and von Willebrand factor are exclusively synthesized in the liver

For SLOW bleeding (<0.5 ml/min): radionucleotide Tc-99m-tagged RBC scan
- For RAPID bleeding (>0.5 ml/min): angiography ± embolization
Table 14. Test of Liver Function

<table>
<thead>
<tr>
<th>Test</th>
<th>What do levels correlate with?</th>
<th>Increased by</th>
<th>How to Interpret</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin Time (PT or INR)</td>
<td>Hepatic protein synthesis All coagulation factors except VIII</td>
<td>Hepatocellular dysfunction Vitamin K deficiency</td>
<td>PT/INR will promptly correct if vitamin K is administered, so increased PT/INR in absence of vitamin K deficiency is a reliable marker of hepatocellular dysfunction</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>Hepatic protein synthesis</td>
<td>Hepatocellular dysfunction Malnutrition Renal or GI losses Significant inflammation Malignancy</td>
<td>Rule out other potential causes</td>
</tr>
<tr>
<td>Serum Direct Bilirubin</td>
<td>Hepatic excretion from hepatocyte to biliary system</td>
<td>Liver dysfunction</td>
<td>Conjugation is preserved even in end stage liver failure, thus increased direct bilirubin indicates liver dysfunction</td>
</tr>
</tbody>
</table>

B. TESTS OF LIVER INJURY

- disproportionately increased AST or ALT = hepatocellular damage
  - ALT more specific to liver; AST from multiple sources (especially muscle)
  - elevation of both highly suggestive of liver injury
  - most common cause of elevated ALT is fatty liver
- disproportionately increased ALP and GGT = cholestasis
  - if ALP is elevated alone, rule out bone disease by fractionating ALP and/or checking GGT
  - if ALP elevation out of proportion to ALT/AST elevation, consider:
    1. obstruction of common bile duct (extraluminal = pancreatic Ca, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, hemihelms)
    2. destruction of microscopic ducts (e.g. PBC)
    3. bile acid transporter defects (drugs, intrahepatic cholestasis of pregnancy)
    4. infiltration of the liver (liver metastases, lymphoma, granulomas, amyloid)

Acute Viral Hepatitis (General)

Definition
- viral hepatitis lasting <6 mo

Clinical Features
- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
- N/V, anorexia, fatigue, myalgia, low-grade fever
- arthralgia and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
- pale stools and dark urine 1-5 d prior to icteric phase
- hepatomegaly and RUQ pain
- splenomegaly and cervical lymphadenopathy (10-20% of cases)

Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP minimally elevated
- viral serology, particularly the IgM antibody directed to the virus

Treatment
- supportive (hydration, diet)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin 20 mg/dL, increased INR, decreased albumin, hypoglycemia

Complications
- hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

Hepatitis A Virus

- RNA virus
- fecal-oral transmission, incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice

Alcoholic hepatitis: history of recent alcohol, RUQ abdominal pain, AST/ALT >2, AST usually <200, low grade fever, mildly elevated WBC

Major Sources of ALP
- Hepatobiliary tree
- Bone
- Placenta

DDx for Hepatomegaly
- Congestive (right heart failure, Budd-Chiari syndrome)
- Infiltrative
  - Malignant (primary, secondary, lymphoproliferative, leukemia)
  - Benign (fatty liver, cysts, hemochromatosis, extramedullary hematopoiesis, amyloid)
- Proliferative
  - Infectious (viral, tuberculosis, abscess, echinococcus)
  - Inflammatory (granulomas [sarcoid], histiocytosis X)

DDx for Hepatitis
- Viral infection
- Alcohol
- Drugs
- Immune-mediated
- Toxins

Causes of Elevated Serum Transaminases in Chronic Hepatitis B
- Ongoing immune-mediated liver injury without immune control of HBV
- Reactivation from prior immune control due to lack of adequate immune control
- Seroconversion (HBeAg converting to anti-HBe, spontaneously or with Rx)
- Hepatitis D
- Other liver insult (fatty liver, alcohol, drugs, hepatitis A)
• can cause acute liver failure and subsequent death (<1-5%)
• can relapse, but never becomes chronic

**Hepatitis B Virus**

**Table 15. Hepatitis B Serology**

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>Anti-HBs</th>
<th>HBeAg</th>
<th>Anti-HBe</th>
<th>Anti-HBc</th>
<th>Liver Enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>IgM</td>
</tr>
<tr>
<td>Chronic (e-Ag positive) HBV (generally high HBV DNA)</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>IgG</td>
<td>ALT, AST elevated</td>
</tr>
<tr>
<td>Chronic (e-Ag negative) HBV (generally low HBV DNA)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>IgG</td>
<td>ALT, AST normal</td>
</tr>
<tr>
<td>Resolved infection</td>
<td>-</td>
<td>±</td>
<td>-</td>
<td>±</td>
<td>IgG</td>
<td></td>
</tr>
<tr>
<td>Immunization</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

**Epidemiology**

• 4 phases of chronic hepatitis B: not all will go through all 4 phases, but all will have positive HBsAg
  1. **immune tolerance**: extremely high HBV-DNA (>20,000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or ‘incubation period’ in adult with newly-acquired HBV)
  2. **immune clearance** (or immunoactive): falling but still elevated HBV-DNA levels (>20,000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment
  3. **immune control**: lower HBV-DNA (<20,000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy
  4. **immune escape** (“core or precore mutant”); elevated HBV-DNA (>2,000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

**Management**

• counseling: 40% of men and 10% of women with perinatal infection will die from HBV-related complications
• prolonged immune-mediated damage leads to higher risk of liver fibrosis
• hepatocellular carcinoma screening with ultrasound ≥6mo, especially if high serum HBV-DNA levels, cirrhosis, men, (age >40 in Asian men, >50 in Asian women, and >20 in African descent)
• consider pharmacological therapy if
  1. HBeAg positive + HBV-DNA >20,000 IU/mL + elevated ALT; or
  2. HBeAg negative + HBV-DNA >2,000 IU/mL + elevated ALT + stage ≥2 fibrosis on liver biopsy
• treat to prevent flare when placed on immunosuppressive therapy such as prednisone
• treatment goal: reduce serum HBV-DNA to undetectable level

**Figure 12. Time course of acute hepatitis B infection**

Without treatment, 8-20% of those with ongoing immunoactive chronic hepatitis can develop cirrhosis within 5 yr. In contrast, those in the immune tolerant phase (with extremely high HBV-DNA levels) are at minimal risk for liver fibrosis as they do not have immune-mediated liver injury.

In acute hepatitis B, HDV co-infection increases severity of hepatitis but does not increase risk of progression to chronic hepatitis. However, in the context of chronic hepatitis B, superinfection with HDV increases progression to cirrhosis.
• treatment options: interferon, tenofovir, entacavir, lamivudine, adefovir
• vaccine against HAV if serology negative (to prevent further liver damage)
• follow blood and sexual precautions

**Hepatitis D**
• defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with hepatitis B; causes more aggressive disease than hepatitis B virus alone
• co-infection: acquire HDV and HBV at the same time
  ▪ better prognosis than superinfection (acute HDV infection on pre-existing HBV infection)
• HDV can present as ALF and/or accelerate progression to cirrhosis
• management: low-dose interferon (20% response) and liver transplant for end-stage disease

**Hepatitis C Virus**
• RNA virus
• blood-borne transmission; sexual transmission is “inefficient”
• major risk factor: injection drug use
• other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
• clinical manifestation develops 6-8 wk after exposure
  ▪ symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage

**Diagnosis**
• suspected on basis of elevated ALT/AST and positive serum anti-HCV
• diagnosis established by detectable HCV-RNA in serum
• virus genotype correlates with response to treatment but not prognosis
  ▪ serum HCV-RNA inversely correlates with response to treatment
• normal transaminases can have underlying cirrhosis on biopsy, but otherwise excellent prognosis

**Management**
• blood-borne precautions; vaccinate for hepatitis A and B if serology negative; avoid alcohol
• clearest indication for treatment is in subgroup likely to develop clinically significant liver disease
  ▪ persistently elevated transaminases, liver biopsy shows fibrosis/cirrhosis and at least moderately severe necrosis/inflammation
• indicators of poor response to treatment: cirrhosis, genotype 1, high HCV-RNA, co-infection with HIV, African-American race
• pegylated interferon-α + ribavirin aims to clear HCV infection, but only 50-80% success rate and side effects common (therefore not all patients are treated)
  ▪ sustained virologic response (SVR) = undetectable HCV-RNA 3-6 mo off treatment (which generally means that HCV has been successfully eradicated) = “cure”
  ▪ pegylated interferon-α SC injection weekly and ribavarin PO bid and add protease inhibitor PO (bocepravir or telaprevir) for genotype 1
• length of treatment often determined by rapidity and degree of fall in HCV RNA level
• adverse effects: depression/fatigue, hemolysis, bone marrow suppression (monitor CBC regularly), fevers/myalgia, precipitates autoimmune diseases (rare), skin rashes
• recently introduced protease inhibitors for genotype 1 (most common, least amenable to treatment) have significantly increased sustained remission rate to up to 70%
• interferon-free regimens using combinations (>2) of oral anti-viral drugs have shown high efficacy and will likely be the mainstay of treatment in future years

**Prognosis**
• 80% of acute hepatitis C become chronic (of these 20% evolve to cirrhosis)
• risk of hepatocellular carcinoma increases if cirrhotic
• can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

**Risk Factors for Progression**
• EtOH
• HIV co-infection
• Old age at diagnosis

**HCV treatment lowers the risk of hepatocellular carcinoma**
### Table 16. Characteristics of the Viral Hepatitis

<table>
<thead>
<tr>
<th>Virus Family</th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
<th>CMV</th>
<th>EBV</th>
<th>Yellow Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Environment</td>
<td>Fecal-oral</td>
<td>Parenteral/sexual or equivalent Vertical</td>
<td>Parenteral/sexual (transfusion, IVDU), sexual (&lt;HBV))</td>
<td>Parenteral (blood products, IVDU)</td>
<td>Parenteral (sexual: Africa, Asia, central America, India, Pakistan)</td>
<td>Fecal-oral (endemic)</td>
<td>Close contacts, most body fluids</td>
<td>Saliva-oral</td>
</tr>
<tr>
<td>Incubation</td>
<td>4-6 wk</td>
<td>6 wk-6 mo</td>
<td>2-26 wk</td>
<td>3-13 wk</td>
<td>2-8 wk</td>
<td>20-60 d</td>
<td>30-50 d</td>
<td>3-6 d</td>
</tr>
<tr>
<td>Onset</td>
<td>Usually abrupt</td>
<td>Usually insidious</td>
<td>Insidious</td>
<td>Usually abrupt</td>
<td>Usually abrupt</td>
<td>Variable</td>
<td>Variable</td>
<td>Usually abrupt</td>
</tr>
<tr>
<td>Communicability</td>
<td>2-3 wk in late incubation to early clinical phase</td>
<td>Acute hepatitis in most adults, 10% of children</td>
<td>Chronicity: 5% adults, 90% infants</td>
<td>80%, 20% of whom develop cirrhosis</td>
<td>5%</td>
<td>None</td>
<td>Common;latent</td>
<td>Common;latent</td>
</tr>
<tr>
<td>Serology</td>
<td>Anti-HAV (IgM)</td>
<td>See Table 15</td>
<td>HCV-RNA Anti-HEV (IgG/IgM)</td>
<td>HBsAg Anti-HDV (IgG/IgM)</td>
<td>Anti-HEV (IgG/IgM)</td>
<td>Anti-CMV (IgG/IgM)</td>
<td>Monospot; anti-IVDUB IgG/ IgG, EBV DNA quantitation</td>
<td>Anti-YF (IgG/IgM)</td>
</tr>
<tr>
<td>Immunity</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Harris, 2 doses q6mo, combined with Twinrix at 0, 7, and 21 d</td>
<td>Recombivax HBTM, age 11-15, 2 doses q6mo</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>YF-VAX, 1 dose booster q10yr</td>
</tr>
<tr>
<td>Management</td>
<td>General hygiene, no vaccine</td>
<td>Prophylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune</td>
<td>Prevention: HBV vaccine and/or hepatitis B lg (HBIG) for needlestick, sexual contact, infants of infected mothers</td>
<td>Prevention: no vaccine Rx: IFN + ribavirin + protease inhibitor; possibility of interferon-free regimens in near future</td>
<td>Prevention: HBV vaccine</td>
<td>Prevention: general hygiene, no vaccine</td>
<td>Supportive treatment post infection</td>
<td>Prevention</td>
</tr>
<tr>
<td>Acute Mortality</td>
<td>0.1-0.3%</td>
<td>0.5-2%</td>
<td>1%</td>
<td>2-20% coinfection with HBV, 30% superinfection</td>
<td>1-2% overall, 10-20% in rare in immunocompetent adults</td>
<td>Rare</td>
<td>Rare</td>
<td>20-60% in developing countries</td>
</tr>
<tr>
<td>Oncogenicity</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Complications</td>
<td>Can cause acute liver failure and subsequent death (&lt;1-5%)</td>
<td>Hepatocellular carcinoma secondary to cirrhosis, serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda</td>
<td>Hepatocellular carcinoma in 2-5% of cirrhosis per yr, cryoglobulinemia, B-cell non-Hodgkin lymphoma</td>
<td>Leukocytoclastic vasculitis, membranous glomerulonephropathy</td>
<td>Mild, except in third trimester (10-20% fulminant liver failure)</td>
<td>5% of newborns with multiple handicaps</td>
<td>Associated with Burkitt’s lymphoma and nasopharyngeal carcinoma (rare in Western world)</td>
<td>Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates</td>
</tr>
</tbody>
</table>

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**Autoimmune Chronic Active Hepatitis**

- diagnosis of exclusion: rule out viruses, drugs, metabolic, or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrahepatic manifestations
  - sicca, Raynaud’s, thyroiditis, Sjögren’s, arthralgias
  - hypergammaglobulinemia
    - anti-smooth muscle antibody elevation is most characteristic; also elevations in anti-LKM (liver kidney microsome, especially in children)
    - less specific: elevated ANA, RF
  - can have false positive viral serology (especially anti-HCV)
  - biopsy – perportal (zone 1) and interface inflammation and necrosis
management: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

### Drug-Induced Liver Disease

#### Table 17. Classification of Hepatotoxins

<table>
<thead>
<tr>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen, CCl₄</td>
<td>Phenytoin, INH</td>
</tr>
<tr>
<td>Usual</td>
<td>Unusual</td>
</tr>
<tr>
<td>Hours-days</td>
<td>Weeks-months</td>
</tr>
<tr>
<td>Not important</td>
<td>Very important</td>
</tr>
<tr>
<td>Yes</td>
<td>No (idiosyncratic)</td>
</tr>
</tbody>
</table>

#### Specific Drugs

- **acetaminophen**
  - metabolized by hepatic cytochrome P450 system
  - can cause ALF (transaminases >1,000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite is formed → covalently binds to hepatocyte membrane
  - presentation
    - first 24 h: N/V (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with ALF or resolution
    - note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy
    - gastric lavage/emesis (if <2 h after ingestion)
    - oral activated charcoal
    - N-acetylcysteine (NAC, Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given no matter when time of ingestion)
      - promotes hepatic glutathione regeneration
      - no recorded fatal outcomes if NAC given before increase in transaminases

- **chlorpromazine**: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus, and eosinophilia

- **INH (isoniazid)**
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age

- **methotrexate**
  - causes fibrosis/cirrhosis; increased risk in the presence of obesity, DM, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment

- **amiodarone**: can cause same histology and clinical outcome as alcoholic hepatitis

- **others**: azoles, statins, methylxanthines, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines

- **herbs**: chaparral, Chinese herbs (e.g. germander, comfrey, bush tea)

### Wilson’s Disease

**Definition**
- autosomal recessive defect in copper metabolism (gene ATP7B)

**Pathology**
- decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin

**Clinical Manifestations**
- liver: acute hepatitis, acute liver failure, chronic active hepatitis, cirrhosis, low risk of hepatocellular carcinoma
- eyes: Kayser-Fleischer rings (copper deposits in Descemet’s membrane); more common in patients with CNS involvement, present in 50% if only liver involvement
- CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
- kidneys: Fanconi’s syndrome (proximal tubule transport defects) and stones

**Clinical Manifestations of Wilson’s Disease**

**ABCD**
- Asterisk
- Basal ganglia degeneration: suspect if parkinsonian features in the young
- Ceruloplasmin ↓
- Cirrhosis
- Corneal deposits (Kayser-Fleischer ring)
- Copper
- Dementia
• blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
• joints: arthritis, bone demineralization, calcifications

**Investigations**
• suspect if increased liver enzymes with clinical manifestations at young age (<30); especially combination of liver disease with dystonia, psychiatric symptoms
• screening tests
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion
• gold standard
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible

**Treatment**
• 4 drugs available
  1. penicillamine chelates copper; poorly tolerated
  2. trientine chelates copper
  3. zinc impairs copper excretion in stool/decreases copper absorption from gut
  4. tetrathiomolybdate preferred if neurological involvement
• screen relatives
• liver transplant in severe cases

---

**Hemochromatosis**

**Definition**
• excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body stores of iron increased to 20–40 g (normal 1 g)

**Pathology**
• primary hemochromatosis
  ▪ primarily due to common recessive gene (HFE, 5%); 1/400 patients are homozygotes
  ▪ results in ongoing gut absorption of iron despite adequate iron stores
• secondary hemochromatosis
  ▪ parenteral iron overload (e.g. transfusions)
  ▪ chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
  ▪ excessive iron intake

**Clinical Manifestations**
• usually presents with trivial elevation in serum transaminases
• liver: cirrhosis (30%), HCC (200x increased risk) – most common cause of death (1/3 of patients)
• pancreas: DM, chronic pancreatitis
• skin: bronze or gray (due to melanin, not iron)
• heart: dilated cardiomyopathy
• pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
• joints: arthralgia (any joint, but especially MCP joints), chondrocalcinosis

**Investigations**
• screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
  ▪ transferrin saturation (free Fe²⁺/TIBC) >45%
  ▪ serum ferritin >400 ng/mL
  ▪ HFE gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
• liver biopsy (generally used to detect cirrhosis or if potential for other causes of liver disease)
  ▪ markers of advanced fibrosis: if any of the following are present at the time of diagnosis → age >40, elevated liver enzymes, or ferritin >1000
  ▪ considered if compound heterozygote and potential other cause of liver injury (e.g. fatty liver, etc.)
  ▪ if C282Y/C282Y and no markers of advanced fibrosis, then biopsy generally not needed
• HCC screening if cirrhosis

**Treatment**
• phlebotomy: weekly or q2wk then lifelong maintenance phlebotomies q2-6mo
• deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
• primary hemochromatosis responds well to phlebotomy
• secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)
Alcoholic Liver Disease

Definition
- fatty liver (all alcoholics): always reversible if alcohol stopped
- alcoholic hepatitis (35% of alcoholics): usually reversible if alcohol stopped
- cirrhosis (10-15% of alcoholics): potentially irreversible

Pathology
- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde
  - reduces NAD+ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- ethanol increases gut permeability leading to increased bacterial translocation
- alcohol metabolism causes
  - relative hypoxia in liver zone III > zone I
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

Clinical Manifestation
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10 to 20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not accurately predict type of liver involvement
  - fatty liver
    - mildly tender hepatomegaly; jaundice rare
    - mildly increased transaminases <5x normal
  - alcoholic hepatitis
    - variable severity: mild to fatal liver failure
    - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice and mildly elevated INR)
    - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased white blood cell count – mimics RLL pneumonia and cholecystitis

Investigations
- blood tests are non-specific, but in general:
  - AST:ALT >2:1 (usually <300)
  - increased GGT
  - CBC: increased MCV (mean corpuscular volume), increased WBC

Treatment
- alcohol cessation (see Psychiatry, PS19)
  - Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
- multivitamin supplements (especially thiamine)
- caution with drugs metabolized by the liver
  - prednisone 40 mg OD x 28 d (taper over 2-4 wk) in subgroup with elevated bilirubin and INR, or if encephalopathy; but contraindicated in GI bleeding, renal failure, infection, pancreatitis
  - response (and subsequent decision to continue treatment) predicted by day 7 bilirubin (Lille score)
- pentoxyphilline decreases TNF, shown in one trial to reduce death, albeit only from renal failure; favorable side-effect profile

Prognosis
- prognosis: Maddrey’s discriminant function (based on PT and bilirubin) predicts mortality
  - fatty liver: complete resolution with cessation of alcohol intake
  - alcoholic hepatitis mortality
    - immediate: 30%-60% in the first 6 mo if severe
    - with continued alcohol: 70% in 5 yr
    - with cessation: 30% in 5 yr
  - alcoholic hepatitis DM
Non-Alcoholic Fatty Liver Disease

Definition
• spectrum of disorders characterized by macrovesicular hepatic steatosis
• most common cause of liver disease in North America

Pathology
• pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
• changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

Risk Factors
• likely a component of the metabolic syndrome along with type 2 DM, HTN, hypertriglyceridemia
• rapid weight loss or weight gain

Clinical Manifestations
• often asymptomatic
• may present with fatigue, malaise, and vague RUQ discomfort
• elevated serum triglyceride/cholesterol levels and insulin resistance

Investigations
• elevated serum AST, ALT ± ALP; AST/ALT <1
• presents as echogenic liver texture on ultrasound
• liver biopsy diagnostic, but often necessary only for prognosis

Treatment
• no proven effective therapy other than gradual weight loss
• some evidence for vitamin E (800 U daily) in select groups
• pioglitazone can be considered if DM concomitantly present, but results in weight gain
• modification of risk factors is generally recommended, especially gradual weight reduction
• optimization of therapy for DM, hyperlipidemia, HTN

Prognosis
• most die from cardiovascular or cerebrovascular disease
• better prognosis than alcoholic hepatitis
  • <25% progress to cirrhosis over a 7-10 yr period
• risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
• other clinical indicators of unfavorable prognosis: DM, age, metabolic syndrome

Acute Liver Failure (formerly Fulminant Hepatic Failure)

Definition
• severe decline in liver function characterized by coagulation abnormality (INR>1.5) and encephalopathy
• in setting of previously normal liver
• rapid (<26 wk duration)

Pathology
• drugs (especially acetaminophen), hepatitis B (measure IgM anti-HBc because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic

Treatment
• correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, monitor for infection and multiorgan failure (usually requires ICU)
• consider liver biopsy before INR becomes too high
• chief value is to exclude chronic disease, less helpful for prognosis
• liver transplant (King’s College criteria can be used as prognostic indicator): consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), age <10 or >40, cause is drug or unknown, bilirubin >17.5 mg/dL, INR >3.5, creatinine >2.6 mg/dL
Cirrhosis

Definition
- liver damage characterized by diffuse distortion of the basic architecture and replacement with scar tissue and formation of regenerative nodules
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 yr with almost normal life expectancy
- Stage 2 cirrhosis is the onset of first decompensation, typically development of ascites (most common), variceal bleeding, encephalopathy

Pathology
- fatty liver (alcohol, non-alcoholic fatty liver disease)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- hemochromatosis
- primary biliary cirrhosis
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- cryptogenic (i.e. no identifiable cause, although many of these patients may represent 'burnt-out NASH')
- rare: Wilson's disease, Gaucher's disease, α1-antitrypsin deficiency

Investigations
- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive:
  - blood work: fall in platelet count <150 is the earliest finding, followed many yr later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event; see Figure 13)
  - FibroTest: combination of various clinical and biochemical markers that can predict degree of fibrosis
  - imaging:
    - U/S is the primary imaging modality but only finds advanced cirrhosis
    - CT to look for varices, nodular liver texture, splenomegaly, ascites
    - FibroScan: non-invasive tool using elastography (variable availability)
    - gastroscopy: varices or portal gastropathy

Treatment
- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs, immunize for Hep A and B if non-immune)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score and MELD score
- liver transplantation for end-stage disease if no alcohol for >6 mo; use MELD score

Table 18. Child-Pugh Score and Interpretation

<table>
<thead>
<tr>
<th>Classification</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (mg/dL)</td>
<td>&lt;2</td>
<td>2-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Serum albumin (g/dL)</td>
<td>&gt;3.5</td>
<td>2.8-3.5</td>
<td>&lt;2.8</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>Absent</td>
<td>Controllable</td>
<td>Refractory</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Absent</td>
<td>Minimal</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Interpretation
- Points | Class | Life Expectancy | Perioperative Mortality |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>15-50 yr</td>
<td>10%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>Candidate for transplant</td>
<td>30%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>1-3 mo</td>
<td>82%</td>
</tr>
</tbody>
</table>

Score: 5-6 (Child’s A), 7-9 (Child’s B), 10-15 (Child’s C)

*Note: Child’s classification is rarely used for shunting, but is still useful to quantitate the severity of cirrhosis
Complications

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR
  - relationship of INR to bleeding tendency is controversial; some patients may be hypocoagulable, others may be hypercoagulable
- variceal bleeds
  - half of patients with cirrhosis have gastroesophageal varices and one-third of these develop hemorrhage with an overall mortality of >30%
  - hepatic venous pressure gradient (HVPG) ≥10 mmHg is the strongest predictor of variceal development
  - management: resuscitation, antibiotic prophylaxis, vasoactive drugs (e.g. octreotide IV) combined with endoscopic band ligation or sclerotherapy, TIPS
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to over-diuresis)
    - acute tubular necrosis (ATN)
    - hepatorenal syndrome (HRS)
      - Type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - Type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
  - HRS can occur at any time in severe liver disease, especially after:
    - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
    - GI bleed
    - sepsis
  - treatment for hepatorenal syndrome (generally unsuccessful at improving long-term survival)
    - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
    - definitive treatment is liver transplant
- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal HTN
  - thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators vs. production of a vasodilating substance by the liver
  - clinical features
    - hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency) and orthodeoxia (desaturation in the upright position, improved by recumbency),
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation

Hepatocellular Carcinoma

- see General Surgery, GS43

Liver Transplantation

- see General Surgery, GS44
Portal Hypertension

**Definition**
- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

**Pathophysiology**
- 3 sites of increased resistance (remember pressure = flow x resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constrictive pericarditis)

**Complications**
- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

**Management**
- non-selective β-blockers (propanolol, nadolol) decrease risk of bleeding from varices
- TIPS: to decrease portal venous pressure
  - shunt between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute bleeding or prevent rebleeding or treat ascites
  - shunt usually remains open for <1 yr
- complications: hepatic encephalopathy, deterioration of hepatic function
- contraindicated with severe liver dysfunction
- most commonly used as a "bridge" to liver transplant
- other surgically created shunts (rare): portacaval, distal spleno-renal (Warren shunt)

Hepatic Encephalopathy

**Definition**
- spectrum of potentially reversible neuropsychiatric syndromes secondary to liver disease diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

**Pathophysiology**
- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain

**Precipitating Factors**
- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

**Stages**
- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar responses
- IV: coma (response to painful stimuli only)

**Investigations**
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hypoponatremia, hypoglycemia)
  - characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves
Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - decrease dietary protein to 50 g/d; vegetable protein is better tolerated than animal protein
  - lactulose: titrated to achieve 2 to 3 soft stools per day
    - prevents diffusion of NH₃ (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH₄ (ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
  - if inadequate response with lactulose may try antibiotics
    - broad-spectrum antibiotics (metronidazole, rifaximin) eliminate ammonia producing bacteria from bowel lumen
  - non-absorbable antibiotic rifaximin probably most effective treatment
- best acute treatment in comatose patient is lactulose enemas

Ascites

Definition
- accumulation of excess fluid in the peritoneal cavity

Etiology

Table 19. Serum-Ascites Albumin Gradient as an Indicator of the Causes of Ascites

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis/severe hepatitis</td>
<td>&gt;11 g/L (1.1 g/dL)</td>
<td>Serum [Alb] – Ascitic [Alb] &lt;11 g/L (1.1 g/dL)</td>
<td>Portale carcinomatosis</td>
</tr>
<tr>
<td>Chronic hepatic congestion (right heart failure, Budd-Chiari)</td>
<td></td>
<td></td>
<td>TB</td>
</tr>
<tr>
<td>Massive liver metastases</td>
<td></td>
<td></td>
<td>Pancreatic disease</td>
</tr>
<tr>
<td>Myxedema</td>
<td></td>
<td></td>
<td>Serosis</td>
</tr>
</tbody>
</table>

* In nephrotic syndrome: decreased serum [Alb] to begin with therefore gradient not helpful

Pathogenesis
- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis: first step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchnic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney
  - overfill hypothesis: cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily
  - peripheral arterial vasodilation theory (most popular): as portal HTN develops in cirrhosis, production of local mediators such as nitric oxide lead to splanchnic arterial vasodilation which ultimately results in reduction of effective arterial volume and compensatory sodium and fluid retention by the kidneys (i.e. circulation volume is increased, as per overflow hypothesis, but relatively underfilled, as per underfill hypothesis)

Diagnosis
- abdominal ultrasound
- physical exam (clinically detectable when >500 mL)
  - bulging flanks, shifting dullness, fluid-wave test positive
  - most sensitive symptom: ankle swelling

Investigations
- diagnostic paracentesis
  - 1st aliquot: cells and differential
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis; TG and chylomicrons if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis

Gastroenterology 2007;133:818-824

Study: RCT, double-blinded study with 1 yr follow-up.

Population: 68 patients with cirrhosis, ascites, ascitic fluid protein <1.5 g/dL, and impaired renal function or severe liver failure.

Intervention: General, regional, or combined anesthesia to patients undergoing a surgical procedure.

Main Outcome: Norfloxacin vs. placebo.

Results: There was a significant reduction of patients developing spontaneous bacterial peritonitis (SBP) (6% vs. 30%, p=0.02) and spontaneous bacteremia (6% vs. 12%, p=0.05) with norfloxacin therapy. There were significantly fewer patients who developed all-cause renal failure (7 vs. 16, p=0.03) and hepaticorenal syndrome (HRS) with norfloxacin therapy. Probability of survival at 3 mo (94% vs. 62%, p=0.02) and 1 yr (60% vs. 40%, p=0.003) were high in patients treated with norfloxacin.

Conclusion: Primary prophylaxis with norfloxacin in patients with advanced cirrhosis reduced SBP, HRS, and improved 1 yr survival.
therapeutic/palliative paracentesis indicated
- IV albumin (not indicated if <5 L removed by paracentesis)
- TIPS in an appropriate patient (no contraindications) with potential transplant-free survival advantage
- liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis are associated with 50% 2 yr mortality

Complication: Primary/Spontaneous Bacterial Peritonitis
- primary/spontaneous bacterial peritonitis (SBP)
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: E. coli (most common), Streptococcus, Klebsiella

  - diagnosis
    - absolute neutrophil count in peritoneal fluid >0.25x10^6 cells/L (250 cells/mm³)
    - Gram stain positive in only 10-50% of patients
    - culture positive in <80% of patients (not needed for diagnosis)
  - prophylaxis: consider in patients with:
    - cirrhosis or GI bleed: ceftriaxone IV daily or norfloxacin bid x 7 d
    - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
  - treatment
    - IV antibiotics (cefotaxime 2 g IV q8h or ceftriaxone 2g IV daily is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
    - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

Biliary Tract

Jaundice
- see Table 2, G6 and Figures 15 and 16, G42

Signs and Symptoms
- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic tumor (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer
- kernicterus: rarely seen in adults due to maturation of blood brain barrier

Investigations
- blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
- U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
- direct bile duct visualization
  - magnetic resonance cholangiopancreatography (MRCP): non-invasive
  - endoscopic ultrasound (EUS): sensitive for stones and pancreatic tumors
  - endoscopic retrograde cholangiopancreatography (ERCP): invasive, most accurate, allows for therapeutic intervention
  - percutaneous transhepatic cholangiography (PTC): if ERCP fails, if obstruction is in liver
**Gilbert’s Syndrome**

**Definition**
- Mild decrease in glucuronyltransferase activity leading to defective conjugation of bilirubin.

**Etiology/Epidemiology**
- Some patients have decreased hepatobiliary uptake.
- Affects 7% of the population, especially males.
- Autosomal dominant, 70% due to a mutation in the UGT gene.

**Signs and Symptoms**
- Presents in teens-20s, often an incidental finding.
- Only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting, or at times of acute illness; no other clinical implications.

**Treatment**
- None indicated (entirely benign).

---

**Sclerosing Cholangitis**

**Definition**
- Inflammation of biliary tree (intra and/or extrahepatic bile ducts) leading to scarring and lumen obliteration.

**Etiology**
- Primary/idiopathic (most common)
  - Associated with IBD, more commonly UC, in up to 70% of patients (usually male).
  - One of the most common indications for transplant.
- Secondary (less common)
  - Long-term choledocholithiasis.
  - Cholangiocarcinoma.
  - Surgical/traumatic injury (iatrogenic).
  - Contiguous inflammatory process.
  - Post-ERCP.
  - Associated with HIV/AIDS (“HIV cholangiopathy”).
  - IgG4-related disease.

**Signs and Symptoms**
- Often insidious, may present with fatigue and pruritus.
- May present with signs of episodic bacterial cholangitis secondary to biliary obstruction.

**Diagnosis**
- Increased ALP (hallmark), less often increased bilirubin.
- Mildly increased AST, usually <300 U/L.
- p-ANCA (30-80%), elevated IgM (40-50%).
ERCP shows narrowing and dilatations of bile ducts that may result in “beading”, both intrahepatic and extrahepatic bile ducts
  - if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC

Complications
- repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
- increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat

Management
- image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma (controversial)
- endoscopic sphincterotomy, biliary stent in selected cases of dominant CBD stricture
- antibiotics for cholangitis
- suppurative cholangitis requires emergency drainage of pus in CBD
- liver transplantation appears the best treatment for advanced sclerosing cholangitis (nearly 90% 1 yr survival; mean follow-up from time of diagnosis to need for transplant is 10 yr)
- ursodiol: previously recommended, but studies suggest that at least in high doses it increases mortality

Prognosis
- unfavorable regardless of treatment
- mean survival after diagnosis remains 4-10 yr

Primary Biliary Cirrhosis

Definition
- chronic inflammation and fibrous obliteration of intrahepatic bile ductules

Etiology/Epidemiology
- likely autoimmune (associated with Sjögren’s syndrome, scleroderma, CREST syndrome, RA, thyroiditis)
- affects mainly middle-aged women (M:F = 1:9)

Signs and Symptoms
- often asymptomatic
- initial symptoms: pruritus, fatigue
- chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
- end-stage: hepatocellular failure, portal HTN, ascites
- high incidence of osteoporosis

Investigations
- increased ALP, GGT; bilirubin rises in later stage
- positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
- increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  - may have: xanthelasmas, xanthomas
- liver biopsy confirms diagnosis and stages severity
- normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
- recently described “overlap” syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis

Clinical Course
- can be fatal, although not all asymptomatic patients show progression

Treatment
- treat with ursodiol (less frequently colchicine, methotrexate)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- monitor for thyroid disease
- liver transplant if disease severe, progressive

Table 20. Primary Sclerosing Cholangitis vs. Primary Biliary Cirrhosis

<table>
<thead>
<tr>
<th>Predominant Gender</th>
<th>Primary Sclerosing Cholangitis</th>
<th>Primary Biliary Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated Comorbidities</td>
<td>IBD, especially UC</td>
<td>Other autoimmune disorders (Sjögren’s, CREST, RA)</td>
</tr>
<tr>
<td>Affecte Ducts</td>
<td>Both intra- and extra-hepatic</td>
<td>Intrahepatic only</td>
</tr>
<tr>
<td>Investigations</td>
<td>ERCP/MRCP (narrowing and dilatations of ducts visualized)</td>
<td>Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)</td>
</tr>
</tbody>
</table>
Secondary Biliary Cirrhosis

Definition
• cirrhosis from prolonged partial or total obstruction of major bile ducts

Etiology
• acquired: post-operative strictures, chronic pancreatitis, sclerosing cholangitis, stone in bile duct
• congenital: CF, congenital biliary atresia, choledochal cysts

Diagnosis
• cholangiography and liver biopsy

Treatment
• treat obstruction, give antibiotics for cholangitis prophylaxis

Biliary Colic, Cholecystitis

• see General Surgery, GS46

Ascending Cholangitis

• see General Surgery, GS48

Definition
• infection of the biliary tree

Etiology
• stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
• infection originates in the duodenum or spreads hematogenously from the portal vein
• bacteria
  ▪ *E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*
  ▪ co-infection with *Bacteroides* and *Clostridia* can occur

Signs and Symptoms
• Charcot’s triad: fever, RUQ pain, jaundice (50-70%)
• Reynold’s Pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

Diagnosis
• increased WBC
• usually increased ALP and bilirubin, ALT variably elevated
• blood culture
• abdominal U/S: CBD dilation, stones

Treatment
• most important is drainage, ideally via ERCP, but if necessary by percutaneous biliary or surgical routes
• antibiotic therapy; broad spectrum to cover Gram-negatives, *Enterococcus*, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  ▪ ampicillin + sulbactam or piperacillin/tazobactam
  ▪ metronidazole + 3rd generation cephalosporin (e.g. ceftriaxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  ▪ carbapenem monotherapy (e.g. imipenem or meropenem)

Prognosis
• good with effective drainage and antibiotics in mild to moderate cases
• high mortality (~50%) in patients with Reynold’s Pentad
Pancreas

Pancreatic Enzyme Abnormalities

Causes of Increased Serum Amylase

- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

Causes of Increased Serum Lipase

- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure

Acute Pancreatitis

Etiology

- Idiopathic: thought to be hypertensive sphincter or microlithiasis
- Gallstones (45%)
- Alcohol (35%)
- Tumors: pancreas, ampulla, choledochocoele
- Scorpion stings
- Microbiological
  - bacterial: Mycoplasma, Campylobacter, TB, M. avium intracellulare, Legionella, leptospirosis
  - viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
  - parasites: ascariasis, clonorchiasis, echinococcosis
- Autoimmune: SLE, polyarteritis nodosa (PAN), Crohn's disease
- Surgery/trauma
  - manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer
- Hyperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), Hypercalcemia, Hypothermia
- Emboli or ischemia
- Drugs/toxins
  - azathioprine, mercaptopurine, furosemide, estrogens, methylprednisolone, H2-blockers, valproic acid, antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

Pathogenesis

- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
- in ethanol-related pancreatitis, pathogenesis is unknown
- in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis, mutation in SPINK 1 gene which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

Pathology

- mild (interstitial)
  - peri-pancreatic fat necrosis
  - interstitial edema
- severe (necrotic)
  - extensive peri-pancreatic and intra-pancreatic fat necrosis
  - parenchymal necrosis and hemorrhage \rightarrow infection in 60%
  - release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
- severity of clinical features may not always correlate with pathology
• 3 phases
  ▪ local inflammation + necrosis → hypovolemia
  ▪ systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
  ▪ local complications 2 wk after presentation → pancreatic sepsis/abscess

Signs and Symptoms
• pain: epigastric, noncolicky, constant
  ▪ may radiate to back
  ▪ may improve when leaning forward (Inglefingen’s sign)
• tenderness:
  ▪ tender rigid abdomen; guarding
  ▪ N/V
  ▪ abdominal distention from paralytic ileus
• fever: chemical, not due to infection
  ▪ jaundice: compression or obstruction of bile duct
  ▪ Cullen’s/Gray-Turner’s signs
  ▪ tetany: transient hypocalcemia
  ▪ hypovolemic shock: can lead to renal failure
  ▪ acute respiratory distress syndrome
  ▪ coma

Investigations
• increased serum pancreatic enzymes: amylase, lipase (more specific)
• ALT >150 specific for biliary cause
• increased WBC, glucose, low calcium
• imaging:
  ▪ CT most useful for diagnosis and prognosis
    ▪ x-ray: ‘sentinel loop’ (dilated proximal jejunum), calcification, and “colon cut-off sign” (colonic spasm)
  ▪ U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  ▪ CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  ▪ ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumor,
  ▪ perianal edema
  ▪ aspiration biopsy (see sidebar)

Prognosis
• usually a benign, self-limiting course, single or recurrent
• occasionally severe leading to:
  ▪ shock
  ▪ pulmonary edema
  ▪ multi-organ dysfunction syndrome
  ▪ GI ulceration due to stress
  ▪ death
• mortality according to Ranson’s criteria (see sidebar)
  ▪ ≤2 criteria = <5% mortality
  ▪ 3–4 criteria = 15–20%
  ▪ 5–6 criteria = 40%
  ▪ ≥7 criteria = >99%
• multiple other prognostic indices available, more accurate than Ranson but difficult to remember (e.g. APACHE)

Treatment
• goals (only supportive therapy available)
  (1) hemodynamic stability
  (2) analgesia
  (3) oxygen
  (4) stop progression of damage (difficult)
  (5) treat local and systemic complications
• antibiotics controversial except in documented infection (use cephalosporins, imipenem)
• aspirate necrotic areas of pancreas to diagnose infection; drain if infected
• IV fluids (crystalloid or colloid)
• NG suction (reduces pressure)
• nutritional support:
  ▪ nasojejunal feeding tube or TPN if cannot tolerate enteric feeds
  ▪ recent evidence supports nasogastric enteral (or oral if feasible) feeds
  ▪ no benefit: glucagon, atropine, aprotinin, H2-blockers, peritoneal lavage
• follow clinically and CT/ultrasound to exclude complications
• chief role of surgery is to drain fluid or excise necrotic tissue (necrosectomy) in the case of infected necrotic tissue (try to delay for >2 wk to allow demarcation between viable and necrotic tissue)

Ranson’s Criteria: Prognostic Indicator of Mortality in Pancreatitis not due to Gallstones

At Admission
G: Blood Glucose > 11 mmol/L (> 200 mg/dL) (with no history of hyperglycemia)
A: Age > 55
L: Serum LDH > 350 IU/L
H: ALP > 350 IU/L
W: WBC > 16 x 109/L (16,000/mm3)

During First 48 h
C: Serum Calcium < 2 mmol/L (< 8 mg/dL)
T: Hematocrit drop > 10%
O: Arterial P O2 < 60 mmHg
N: Base deficit > 6 mmol/L (> 4 mEq/L)
E: BUN rise > 1.8 mmol/L (> 5 mg/dL)
S: Estimated fluid Sequestration > 6 L

• Difficult course if 2 criteria present
• High mortality if ≥ 3 criteria present

Note:
• coma
• acute respiratory distress syndrome
• hypovolemic shock: can lead to renal failure
• tetany: transient hypocalcemia
• coma
• multi-organ dysfunction syndrome
• hypovolemic shock: can lead to renal failure
• fever: chemical, not due to infection

Increased Amylase
• Sensitive, not specific

Increased Lipase
• Higher sensitivity and specificity
• Stays elevated longer

References:
Am J Gastroenterol 2008;103:104-110
Gastroenterology Pancreas Essential Med Notes 2015
Late Complications
- pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  - drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
- infected necrosis/abscesses: antibiotics + percutaneous drainage, endoscopic vs. surgical
- bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
- splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
- rare: DM, pancreatic duct damage

Chronic Pancreatitis

Definition
- irreversible damage to pancreas characterized by:
  1. pancreatic cell loss (from necrosis)
  2. inflammation
  3. fibrosis

Etiology/Pathophysiology
- alcohol (most common)
  - causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
  - changes composition of pancreatic juice (e.g. increases viscosity)
  - decreases pancreatic secretion of pancreatic stone protein (lithostathine) which normally solubilizes calcium salts
    - precipitation of calcium within pancreatic duct results in duct and gland destruction
  - toxic effect on acinar and duct cells – directly or via increasing free radicals
  - acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
  - varying degrees of ductular dilatation, strictures, protein plugs, calcification
  - no satisfactory theory to explain why only a minority of alcoholics develop pancreatitis
- unusual causes
  - CF
  - severe protein-calorie malnutrition
  - hereditary
  - idiopathic

Signs and Symptoms
- early stages
  - recurrent attacks of severe abdominal pain (upper abdomen and back)
  - chronic painless pancreatitis: 10%
- late stages: occurs in 15% of patients
  - malabsorption syndrome when >90% of function is lost, steatorrhea
  - DM, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed

Investigations
- laboratory
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
- AXR: pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts
- 72 h fecal fat test: measures exocrine function
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
- fecal pancreatic enzyme measurement (elastase-1, chymotrypsin): available only in selected centers

Management
- most common problem is pain, difficult to control
- general management
  - total abstinence from alcohol
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas “burns out”
- endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct

Gallstones only cause acute pancreatitis (not chronic pancreatitis)

Symptoms of Chronic Pancreatitis
- Abdominal pain
- Diabetes
- Steatorrhea

Etiology = Almost Always Alcohol

Treatment
- Alcohol abstinence
- Pancreatic enzyme replacement
- Analgesics
- Pancreatic resection if ductular blockage

Gallstones only cause acute pancreatitis (not chronic pancreatitis)
• surgery: drain pancreatic duct (pancreaticojejunostomy) if duct dilated (more effective than endoscopy); resect pancreas if duct contracted
• steatorrhea
  ▪ pancreatic enzyme replacement
  ▪ restrict fat, increase carbohydrate and protein (may also decrease pain)
  ▪ neither endoscopy nor surgery can improve pancreatic function

**Autoimmune Pancreatitis**

• most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice ± abdominal pain)

**Investigations**

• histology: lymphocyte and plasma cell infiltration of pancreas
• imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage shaped, low density rim around pancreas
• serology: increased serum IgG4
• other organs involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

**Treatment**

• responds to prednisone

**Clinical Nutrition**

**Determination of Nutritional Status**

• corrected weight loss (expressed as body mass index [kg/m²]) is most important parameter in assessing need for nutritional support

**Investigations**

• plasma proteins: albumin, pre-albumin (shorter half life than albumin), transferrin
  ▪ decrease may indicate decreased nutritional status or disease state
• thyroid-binding globulin, retinol-binding protein (may be too sensitive)
• anthropometry (e.g. triceps skinfold thickness), grip strength less often used

**Table 21. Areas of Absorption of Nutrients**

<table>
<thead>
<tr>
<th></th>
<th>Fe</th>
<th>CHO</th>
<th>Proteins, Lipids</th>
<th>Na⁺, H₂O</th>
<th>Bile Acids</th>
<th>Vit B₁₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Jejunum</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ileum</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

**Enteral Nutrition**

**Definition**

• enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
• choice of tubes: nasogastric (NG), nasojejunal (NJ), percutaneous endoscopic gastrostomy (G-tube), percutaneous endoscopic jejunostomy (J-tube) or tubes can be placed radiologically, surgically

**Indications**

• oral feeding inadequate or contraindicated

**Feeds**

• polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fiber
• elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolarity)
• specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

**Relative Contraindications**

• non-functioning gut (e.g. intestinal obstruction, enteroenteral or entero-cutaneous fistulae)
• uncontrolled diarrhea
• GI bleeding

Hypomagnesemia may be an initial sign of short bowel syndrome in patients who have undergone surgical bowel resection.

Most Common Indications for Artificial Nutrition Support:

• Preexisting nutritional deprivation
• Anticipated or actual inadequate energy intake by mouth
• Significant multiorgan system disease
Complications

- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)

Enteral Nutrition Advantages over Parenteral Nutrition

- far fewer serious complications (especially sepsis)
- nutritional requirements for enteral administration better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Parenteral Nutrition

Definition

- parenteral nutrition is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications

- short-term (<1 mo)
  - whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively, and in difficult to control sepsis
  - pre-operative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)
  - some evidence for efficacy, but convincing data not available for:
    - radiation/chemotherapy-induced enteritis
    - AIDS with wasting diarrhea
    - severe acute pancreatitis
- long-term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of bowel (e.g. bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

Relative Contraindications

- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem
- unreliable patient or clinical setting

Complications of PN

- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: CHF, hyperglycemia, gallstones, cholestasis

Whenever possible, enteral nutrition is ALWAYS preferable over parenteral nutrition
# Common Medications

## Table 22. Common Drugs Prescribed in Gastroenterology

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitors</td>
<td>omeprazole</td>
<td>Losec®/Prilosec®</td>
<td>20 mg PO OD</td>
<td>Inhibits gastric enzymes H⁺/K⁺-ATPase (proton pump)</td>
<td>Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, Zollinger-Ellison syndrome, eradication of H. pylori (combined with antibiotics)</td>
<td>Hypersensitivity to drug</td>
<td>Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)</td>
</tr>
<tr>
<td></td>
<td>lansoprazole or</td>
<td>Prevacid®</td>
<td>Oral therapy: 15-30 mg OD (before breakfast)</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>dexlansoprazole</td>
<td>Dexilant®</td>
<td>IV therapy: 30 mg OD</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>pantoprazole</td>
<td>Pantoloc®/Protonix®</td>
<td>40 mg PO OD for UGIB: 80 mg IV bolus then 8 mg/h infusion</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>rabeprazole</td>
<td>Pariet®/Aciphex®</td>
<td>40 mg PO OD</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>esomeprazole</td>
<td>Nexium®</td>
<td>20-40 mg PO OD</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Histamine H₂-Receptor</td>
<td>ranitidine</td>
<td>Zantac®</td>
<td>300 mg PO OD or 150 mg bid</td>
<td>Inhibits gastric histamine H₂-receptors</td>
<td>Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD, Zollinger-Ellison syndrome</td>
<td>Hypersensitivity to drug</td>
<td>Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression</td>
</tr>
<tr>
<td>Antagonists</td>
<td>famotidine</td>
<td>Pepcid®</td>
<td>Oral therapy: duodenal/gastric ulcers: 40 mg qhs GERD: 20 mg bid IV therapy: 20 mg bid</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Stool Softener</td>
<td>docusate sodium</td>
<td>Colace®</td>
<td>100-400 mg PO OD, divided in 1-4 doses</td>
<td>Promotes incorporation of water into stool</td>
<td>Relief of constipation</td>
<td>Presence of abdominal pain, fever, N/V</td>
<td>Throat irritation, abdominal cramps, rashes</td>
</tr>
<tr>
<td>Osmotic Laxatives</td>
<td>lactulose</td>
<td>Lactulose/Constulose®</td>
<td>Constipation: 15-30 mL PO OD bid</td>
<td>Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid into colon, increases osmotic colonic contents, increases stool volume</td>
<td>Chronic constipation, prevention and treatment of portal-systemic encephalopathy</td>
<td>Patients who require a low galactose diet</td>
<td>Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage</td>
</tr>
<tr>
<td></td>
<td>Peg3350</td>
<td>Lax-a-day®/Golytely®</td>
<td>Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD</td>
<td>Osmotic agent causes water retention in stool and promotes frequency of stool</td>
<td>Relief of constipation</td>
<td>Colonoscopy prep</td>
<td>Hypersensitivity to drug</td>
</tr>
<tr>
<td>Prokinetic Laxatives</td>
<td>senna</td>
<td>Senokot®</td>
<td>Tablets: 1-4 PO qhs</td>
<td>Induce peristalsis in lower colon</td>
<td>Constipation</td>
<td>Patients with acute abdomen</td>
<td>Abdominal cramps, discoloration of breast milk, urine, feces, melanosist coli and atomic colon from prolonged use (controversial)</td>
</tr>
<tr>
<td></td>
<td>bisacodyl</td>
<td>Bisacodyl®</td>
<td>5-30 mg PO OD (start at 10 mg for bowel preparation)</td>
<td>Enteric nerve stimulation and local contact-induced secretory effects. Colonic movements</td>
<td>Constipation</td>
<td>Preparation of bowel for procedure</td>
<td>GI obstruction, Gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>metoclopramide</td>
<td>Maxolon®</td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
<td>See anti-emetics</td>
</tr>
<tr>
<td>Bulk Laxatives</td>
<td>psyllium</td>
<td>Metamucil®</td>
<td>2-6 tabs (1 tab = 0.52 g) PO qd-tid prn</td>
<td>Increases stool bulk → water retention in stool</td>
<td>Constipation</td>
<td>Hypersensitivity to drug</td>
<td>GI obstruction, diarrhea, constipation, abdominal cramps</td>
</tr>
</tbody>
</table>
### Table 22. Common Drugs Prescribed in Gastroenterology (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antidiarrheal Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD Agents</td>
<td>mesalamine</td>
<td>Pentasa®</td>
<td>CD: 1 g tid qid</td>
<td>Active UC: 1 g PO qid</td>
<td>IBD</td>
<td>Hypersensitivity to mesalamine salicylates</td>
<td>Abdominal pain, constipation, arthralgia, headache</td>
</tr>
<tr>
<td></td>
<td>Asacol®</td>
<td>Maintenance UC: 1.8 g divided doses daily also as suppositories and enemas</td>
<td></td>
<td>5-ASA: Blocks arachidonic acid metabolism to prostanoids and leukotrienes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>Azulfidine®</td>
<td></td>
<td>3-4 g PO in divided doses</td>
<td>Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component</td>
<td>Colonic disease</td>
<td>Hypersensitivity to sulfasalazine, sulfapyridine, salicylates; intestinal or urinary obstruction, porphyria</td>
<td>Rash, loss of appetite, N/V, headache, oligospermia (reversible)</td>
</tr>
<tr>
<td>prednisone</td>
<td></td>
<td></td>
<td>20-40 mg PO OD for acute exacerbation</td>
<td>Anti-inflammatory</td>
<td>Mod-severe CD and UC</td>
<td>Complications of steroid therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Immunosuppressive Agents</strong></td>
<td>6-mercaptopurine</td>
<td>Purinethol®</td>
<td>CD: 1.5 mg/kg/d PO</td>
<td>Immunosuppressive</td>
<td>IBD: active inflammation and to maintain remission</td>
<td>Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents; hypersensitivity to azathioprine, pregnancy</td>
<td>Pancreatitis, bone marrow suppression, increased risk of cancer</td>
</tr>
<tr>
<td>azathioprine</td>
<td>Azasan®</td>
<td></td>
<td>IBID: 2-3 mg/kg/d PO</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade®</td>
<td></td>
<td>5-10 mg/kg IV over 2 h</td>
<td>Antibody to TNF-a</td>
<td>Medically refractory CD</td>
<td>Heart failure, moderate to severe, doses &gt; 5 mg/kg</td>
<td>Reported cases of reactivated TB, PCP, lymphoma, other infections</td>
</tr>
</tbody>
</table>
### Landmark Gastroenterology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALF</td>
<td>Gastroenterology</td>
<td>IV NAC was shown to improve transplant-free survival in patients with early non-acetaminophen related acute liver failure. Later stage disease did not improve with IV NAC</td>
</tr>
<tr>
<td>BISAP</td>
<td>Am J Gastro 2009</td>
<td>Five point scoring system for patients with acute pancreatitis to identify those at increased risk for mortality</td>
</tr>
<tr>
<td>Early combined vs. conventional management in Crohn’s disease</td>
<td>Lancet 2003; 371:660-7</td>
<td>Initiation of more intensive therapy early in Crohn’s disease may be more likely to result in corticosteroid-free remission than conventional therapy</td>
</tr>
<tr>
<td>FAMOUS</td>
<td>Lancet 2009; 374:119-25</td>
<td>Famotidine was effective in preventing gastric and duodenal ulcers, and erosive esophagitis in patients receiving low-dose ASA therapy</td>
</tr>
<tr>
<td>Glucocorticoids and NAC in Alcoholic Hepatitis</td>
<td>NEJM 2011; 355:1781-9</td>
<td>Combination therapy improved 1 mo survival, but not 6 mo survival compared to prednisolone monotherapy</td>
</tr>
<tr>
<td>MELD</td>
<td>Gastroenterology 2002;124:91-6</td>
<td>MELD score can be applied for allocation of donor livers as it accurately predicts 3 mo mortality in patients with chronic liver failure</td>
</tr>
<tr>
<td>SONIC</td>
<td>NEJM 2010; 362:1383-95</td>
<td>In moderate-severe Crohn’s disease, infliximab + azathioprine was more likely to result in corticosteroid-free remission than infliximab monotherapy, Infliximab monotherapy was more effective than azathioprine monotherapy</td>
</tr>
</tbody>
</table>

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Atlas
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Basic Anatomy Review

Lateral Abdominal Wall Layers and their Continuous Spermatic and Scrotal Structures (superficial to deep)
1. skin (epidermis, dermis, subcutaneous fat)
2. superficial fascia
   - Camper’s fascia (fatty) → Dartos fascia
   - Scarpa’s fascia (membranous) → Colles’ superficial perineal fascia
3. muscle (see Figure 2 and Figure 3)
   - external oblique → inguinal ligament → external spermatic fascia and fascia lata
   - internal oblique → cremasteric muscle/fascia
   - transversus abdominis → posterior inguinal wall
4. transversalis fascia → internal spermatic fascia
5. preperitoneal fat
6. peritoneum → tunica vaginalis

Midline Abdominal Wall Layers (superficial to deep)
1. skin
2. superficial fascia
3. rectus abdominis muscle; in rectus sheath, divided by linea alba
   - above arcuate line (midway between symphysis pubis and umbilicus)
     - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
     - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus abdominis aponeurosis
   - below arcuate line
     - aponeuroses of external oblique, internal, oblique, transversus abdominis all pass in front of rectus abdominis
4. arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac)
5. transversalis fascia
6. superficial inguinal ring
   - deep inguinal ring
   - Membranous layer of superficial fascia (Scarpa’s fascia)

Figure 1. Abdominal incisions

- Access to RUG or LUQ contents i.e. gallbladder, spleen
- Access to stomach, duodenum, gallbladder, liver, transverse colon
- Can make similar incision in each quadrant for access to each quadrant’s contents
- Not commonly used
- Post-operative ventral hernias common
- Incision made at outer 1/3 - medial 2/3 border of rectus
- Modification of paramedian but with lower risk of dehiscence or ventral hernia
- Not commonly used
- Access to pelvic organs, sigmoid cecum, and rectum
- Suprapubic incision for access to pelvic cavity
- Access to appendix

Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord
### General Surgery Basic Anatomy Review

**Figure 3. Midline cross-section of abdominal wall**

**Figure 4. Blood supply to the GI tract**

**Venous Flow**

- **Azygos vein**
- **Esophageal vein**
- **Liver**
- **Stomach**
- **Umbilicus**
- **Inferior vena cava**
- **Superior mesenteric vein**
- **Paraumbilical vein**
- **Middle colic vein**
- **Left colic veins**
- **Sigmoid veins**
- **Sigmoid colon**
- **Superior rectal vein**
- **Middle rectal veins**
- **Inferior rectal vein**
- **Appendix**

**Porto-systemic anastomoses:**
1. Esophageal branches of left gastric vein with esophageal veins
2. Paraumbilical veins with subcutaneous veins of anterior abdominal wall
3. Superior rectal vein with middle and inferior rectal veins

**Figure 5. Venous drainage of the GI tract**

- **Celiac trunk (1)**
  - i) Common hepatic artery (2)
  - • Hepatic proper (3)
  - • Left hepatic artery (4)
  - • Right hepatic artery (5)
  - • Gastroduodenal (8)
  - ii) Left gastric artery (6)
  - iii) Splenic artery (9)

- **Superior mesenteric artery (10)**
  - i) Right colic artery (12)
  - ii) Middle colic artery (11)
  - iii) Ileocolic artery (13)
  - iv) Ileal and jejunal branches (14)

- **Inferior mesenteric artery (15)**
  - i) Left colic artery (16)
  - ii) Sigmoid arteries (17)
  - iii) Superior rectal artery (18)

- **Organ Arteries**
  - **Liver**
  - Left and right hepatic (branches of hepatic proper)
  - **Spleen**
  - Splenic
  - **Gallbladder**
  - Cystic (branch of right hepatic artery)
  - **Stomach**
  - 1. Lesser curvature: right and left gastric
  - 2. Greater curvature: right (branch of gastroduodenal) and left (branch of splenic)
  - 3. Fundus: short gastrics (branch of spleen)
  - **Duodenum**
  - 1. Gastroduodenal
  - 2. Pancreaticoduodenals (superior branch of gastroduodenal, inferior branch of superior mesenteric)
  - **Pancreas**
  - 1. Pancreatic branches of splenic
  - 2. Pancreaticoduodenals
  - **Small intestine**
  - 1. Superior mesenteric branches: jejunal, ileal, ileocolic
  - **Large intestine**
  - 1. Superior mesenteric branches: right colic, middle colic
  - 2. Inferior mesenteric branches: left colic, sigmoid, superior rectal
Differential Diagnoses of Common Presentations

Acute Abdominal Pain

- acute abdomen = severe abdominal pain of acute onset and requires urgent medical attention
- in patients with acute abdominal pain, the first diagnoses that you should consider are those requiring potential urgent surgical intervention
- two main patterns constituting urgent general surgery referrals are peritonitis and obstruction

Table 1. Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>RUQ</th>
<th>EPIGASTRIC</th>
<th>LQO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary</td>
<td>Gastrointestinal</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Gastritis</td>
<td>Aortic dissection/ruptured AAA</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>GERD/esophagitis</td>
<td>MI</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>PUD</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>CBD obstruction (stone, tumor)</td>
<td>Pancreatitis</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Mallory-Weiss tear</td>
<td>Gastritis</td>
</tr>
<tr>
<td>Budd-Chiari</td>
<td></td>
<td>PUD</td>
</tr>
<tr>
<td>Hepatic abscess/mass</td>
<td></td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Right subphrenic abscess</td>
<td></td>
<td>Splemic</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td>Splenic infarct/abscess</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td>Splenic</td>
</tr>
<tr>
<td>Presentation of gastric, duodenal, or pancreatic pathology</td>
<td></td>
<td>infarct/abscess</td>
</tr>
<tr>
<td>Hepatic flexure pathology (CRC, subcostal incisional herna)</td>
<td></td>
<td>Splenic</td>
</tr>
<tr>
<td>Genitourinary</td>
<td></td>
<td>rupture</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td></td>
<td>Splenic</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td></td>
<td>aneurysm</td>
</tr>
<tr>
<td>Renal: mass, ischemia, trauma</td>
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<tr>
<td>Cardiopulmonary</td>
<td></td>
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<tr>
<td>RLL pneumonia</td>
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<tr>
<td>Effusion/empyema</td>
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<tr>
<td>CHF (causing hepatic congestion and R pleural effusion)</td>
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<tr>
<td>MI</td>
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<tr>
<td>Pericarditis</td>
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<td>Pleuritis</td>
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<td>Miscellaneous</td>
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<td>Herpes zoster</td>
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<td>Trauma</td>
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<td>Costochondritis</td>
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<td>RLQ</td>
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<tr>
<td>Gastrointestinal</td>
<td>Appendicitis</td>
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</tr>
<tr>
<td>Appendicitis</td>
<td>Early appendicitis, perforated appendicitis</td>
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<tr>
<td>Mesenteric ischemia</td>
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<tr>
<td>Gastroenteritis/colic</td>
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<tr>
<td>Constipation</td>
<td></td>
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<tr>
<td>Bowel obstruction</td>
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<tr>
<td>Pancreatitis</td>
<td></td>
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<tr>
<td>Inflammatory bowel disease</td>
<td></td>
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<tr>
<td>Irritable bowel syndrome</td>
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<tr>
<td>Ogilvie’s syndrome</td>
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<td>Cardiovascular/Hematological</td>
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<td>Aortic dissection/ruptured AAA</td>
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<td></td>
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<tr>
<td>Sickle cell crisis</td>
<td></td>
<td></td>
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<tr>
<td>Gastrointestinal/Gynecological</td>
<td></td>
<td></td>
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<tr>
<td>Perforated ectopic pregnancy</td>
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<td></td>
</tr>
<tr>
<td>PID</td>
<td></td>
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<tr>
<td>Acute urinary retention</td>
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<tr>
<td>Endocrinological</td>
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<td>Carcinoid syndrome</td>
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<td>Diabetic ketoacidosis</td>
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<td>Addisonian crisis</td>
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<td>Hypercalcemia</td>
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<td>Other</td>
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<tr>
<td>Lead poisoning</td>
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<tr>
<td>Tertiary syphilis</td>
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<tr>
<td>SUPRAPUBLIC</td>
<td></td>
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<tr>
<td>Gastrointestinal (see RLQ/LLQ)</td>
<td>Acute appendicitis</td>
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<tr>
<td>Appendicitis</td>
<td>IBD</td>
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<tr>
<td>IBD</td>
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<tr>
<td>Gynecological</td>
<td>Endometriosis</td>
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<tr>
<td>Ectopic pregnancy</td>
<td>Thrombosed/infarcted ovary</td>
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<tr>
<td>PID</td>
<td>Invasive abortion</td>
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<td>Endometriosis</td>
<td>Hydrosalphinx/salpingitis</td>
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<td>Threatened/incomplete abortion</td>
<td>Ovarian torsion</td>
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<tr>
<td>Hydrosalphinx/salpingitis</td>
<td>Hemorrhagic fibroid</td>
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<td>Ovarian torsion</td>
<td>Tubo-ovarian abscess</td>
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<td>Gynecological tumors</td>
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<td>Genitourinary</td>
<td>Cystitis (infectious, hemorrhagic)</td>
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<td>Cystitis</td>
<td>Hydroureter/urinary colic</td>
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<tr>
<td>Ectopic pregnancy</td>
<td>Epididymitis</td>
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<td>Testicular torsion</td>
<td>Acute urinary retention</td>
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<tr>
<td>Extraperitoneal</td>
<td>Rectus sheath hematoma</td>
<td></td>
</tr>
<tr>
<td>Abdominal wall hematoma/abscess</td>
<td>Psoas abscesses</td>
<td></td>
</tr>
</tbody>
</table>

In all patients presenting with an acute abdomen, order the following:

**KEY TESTS FOR SPECIFIC DIAGNOSIS**
- Liver function tests (LFTs) including ALP, ALT, AST, bilirubin
- Amylase/lipase
- Urinalysis
- β-hCG (in women of childbearing age)
- Troponins
- Lactate

**KEY TESTS FOR OR PREPARATION**
- CBC, electrolytes, BUN, creatinine, glucose
- CXR + ECG
- PT/INR and PTT

Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate laparotomy

Localization of Pain
- Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation. Kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain

Referred Pain
- Biliary colic: to right shoulder or scapula
- Renal colic: to groin
- Appendicitis: periumbilical to right lower quadrant (RLQ)
- Pancreatitis: to back
- Ruptured aortic aneurysm: to back or flank
- Perforated ulcer: to RLQ (via right paracolic gutter)
- Hip pain: to groin

Most Common Presentations of Surgical Pain
- Sudden onset with rigid abdomen = perforated viscus
- Pain out of proportion to physical findings = mesenteric ischemia or ischemic bowel
- Vague pain that subsequently localizes = appendicitis or other intra-abdominal process that irritates the parietal peritoneum
- Waves of colicky pain = bowel obstruction

Types of Peritonitis
- Primary peritonitis: spontaneous without clear etiology
- Secondary peritonitis: due to a perforated viscus
- Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms
Abdominal Mass

Table 2. Differential Diagnosis of Abdominal Mass

<table>
<thead>
<tr>
<th>Right Upper Quadrant (RUQ)</th>
<th>Upper Midline</th>
<th>Left Upper Quadrant (LUQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder: cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholecystasis</td>
<td>Pancreas: pancreatic adenocarcinoma, other pancreatic neoplasm, pseudocyst</td>
<td>Spleen: splenomegaly, tumor, abscess, subcapsular splenic hemorrhage, can also present as RLQ mass if extreme splenomegaly</td>
</tr>
<tr>
<td>Biliary tract: Klatskin tumor, choleodochal cyst</td>
<td>Abdominal aorta: AAA (pulsatile)</td>
<td>Stomach: tumor</td>
</tr>
<tr>
<td>Liver: hepatomegaly, hepatitis, abscess, tumor (hepatocellular carcinoma, metastatic tumor, etc.)</td>
<td>Gastric tumor (adenocarcinoma, gastrointestinal stromal tumor, carcinoid tumor), MALT lymphoma</td>
<td>Colon: tumor, constipation</td>
</tr>
<tr>
<td>Colon: tumor, constipation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Right Lower Quadrant (RLQ)</th>
<th>Lower Midline</th>
<th>Left Lower Quadrant (LLQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestine: stool, tumor (CRC), mesenteric adenitis, appendicitis, appendiceal phlegmon or other abscess, typhlitis, intussusception, Crohn’s inflammation</td>
<td>Uterus: pregnancy, leiomyoma (fibroid), uterine cancer, pyometra, hematometra</td>
<td>Intestine: stool, tumor, abscess (see RLQ)</td>
</tr>
<tr>
<td>Ovary: ectopic pregnancy, cyst (physiological vs. pathological), tumor (serous, mucinous, struma ovarii, germ cell, Krukenberg)</td>
<td>GI: bladder distention, tumor</td>
<td>Ovary: see RLQ</td>
</tr>
<tr>
<td>Fallopian tube: ectopic pregnancy, tubo-ovarian abscess, hydrosalpinx, tumor</td>
<td></td>
<td>Fallopian tube: see RLQ</td>
</tr>
</tbody>
</table>

Gastrointestinal Bleeding

- see Gastroenterology.

**Indications for Surgery**

- failure of medical management
- exsanguinating hemorrhage: hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage after initial stabilization procedures (up to two attempts of endoscopic control)
- hypovolemic shock
- prolonged bleeding with transfusion requirement >4 units
- bleeding at rate >1 unit/h

**Surgical Management of GI Bleeding**

- **UGIB**
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia, hypotension, tachycardia)
  - initial management with endoscopy; if fails, then consider surgery
  - note: PUD accounts for approximately 55% of severe UGIB

- **LGIB**
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon
  - may occasionally present with melena
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - 75% of patients will spontaneously stop bleeding, however if bleeding continues barium enema should NOT be performed
  - angiography, RBC scan to determine source as indicated
  - surgery indicated if bleeding is persistent - aimed at removing underlying cause of bleeding
  - obscure bleed may require blind total colectomy if the source is not found

**Table 3. Differential Diagnosis of GI Bleeding**

<table>
<thead>
<tr>
<th>Anatomical Source</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Excess anticoagulation (coumadin, heparin, etc.)</td>
</tr>
<tr>
<td></td>
<td>Excess antiplatelet (clopidogrel, ASA)</td>
</tr>
<tr>
<td>Nose</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophageal varices</td>
</tr>
<tr>
<td></td>
<td>Mallory-Weiss tear</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastritis</td>
</tr>
<tr>
<td></td>
<td>Gastric varices</td>
</tr>
<tr>
<td></td>
<td>Dieulafoy’s lesion</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td></td>
<td>Perforated duodenal ulcer*</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Tumors*</td>
</tr>
<tr>
<td></td>
<td>Ulcers</td>
</tr>
</tbody>
</table>
Table 3. Differential Diagnosis of GI Bleeding (continued)

<table>
<thead>
<tr>
<th>Anatomical Source</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunum and Ileocecal Junction</td>
<td>Meckel’s diverticulum (rare surgical management) Small bowel obstruction Cohlin’s disease* Tuberculosis of ileocecal junction</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>Colorectal cancer* Mesenteric thrombosis/ischemic bowel* Ulcerative colitis* (subtotal colectomy if failure of medical management) Angiodysplasia Diverticulosis (<em>if bleeding is persistent) Cohlin’s disease (less frequently presents with bleeding)</em> Pancolitis (infectious, chemotherpay, or radiation induced) Suture or staple line of a post-gastrointestinal anastomosis</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>Diverticulosis (<em>if bleeding is persistent) Sigmoid cancer</em> Bleeding post-polypectomy Polyps (*if not amenable to colonoscopic polypectomy) Inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td>Rectum and Anus</td>
<td>Hemorrhoids (internal &gt; external) Fissures Rectal cancer* Anal varices Polyps (<em>if not amenable to colonoscopic polypectomy) Cohlin’s or ulcerative colitis</em> Solitary rectal ulcer syndrome</td>
</tr>
</tbody>
</table>

*Managed surgically in most cases

Jaundice

- see Gastroenterology, G41

Pre-Operative Preparations

Considerations
- informed consent (see Ethical, Legal, and Organizational Medicine, ELOAMS)
- screening questionnaire to assess important potential risk factors such as age, exercise capacity, medication use, and allergies
- consults: anesthesia, medicine, as indicated
- NPO for ≥ 6 h prior, activity as tolerated (AAT), vital signs routine (VSR)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule → roughly 100-125 cc/h): normal saline or Ringer’s lactate; bolus to catch up on estimated losses including losses from bowel prep
- appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- review patient’s regular medications including prednisone: consider pre-operative stress dose if prednisone with β-blocker used in past year
- prophylactic antibiotics depending on wound class (within 1 h prior to incision); usually cefazolin (Ancef®) ± metronidazole (Flagyl®)
- consider bowel prep: cleans out bowel and decreases bacterial population
- oral cathartic (e.g. fleet Phosphosoda®) starting previous day
- use in selected cases; current evidence does not support routine use
- consider DVT prophylaxis for all inpatient surgery (heparin)
- do not hold heparin prior to surgery unless epidural is expected
- hold clopidogrel and coumadin 5 to 7 days pre-operative; consider holding ASA (surgeon dependent)
- smoking cessation x 8 wk or more pre-operative can significantly decrease post-operative complications
- remote infection: delay elective surgery until infection controlled

Investigations
- routine pre-operative laboratory investigations for elective procedures should be selective
  - only ASA class and surgical risk have been found to independently predict post-operative adverse effects
- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, BUN, creatinine
- INR/PT, PTT
- ABGs and/or PFTs if predisposed to respiratory insufficiency
- CXR (PA and lateral) if >50 yr old or previously abnormal within past 6 mo
- ECG if >50 yr old or as indicated by history
- β-hCG testing in all women of reproductive age

Drains
- NGT
  - indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, to test anastomosis for leak, feeding (only if necessary due to risk of aspiration → naso-jejunal tube preferable)
Surgical Complications

- general principles in preventing complications during the post-operative period include:
  - frequent examination of the patient (daily or more) and their wound
  - removal of surgical tubes as soon as possible
  - early ambulation
  - monitor fluid balance and electrolytes
  - analgesia - enough to adequately address pain, but not excessive
  - skillful nursing care

Post-Operative Fever

- fever does not necessarily imply infection particularly in the first 24-48 h post-operative
- fever may not be present or is blunted if patient is receiving chemotherapy, glucocorticoids, or immunosuppression
- timing of fever may help identify cause
  - hours after surgery – POD #1 (immediate)
    - inflammatory reaction in response to trauma from surgery
    - reaction to blood products received during surgery
    - malignant hyperthermia
  - POD #1-2 (acute)
    - atelectasis (most common cause of fever in first 48 h after surgery)
    - early wound infection (especially Clostridium, Group A Streptococcus – feel for crepitus and look for “dishwater” drainage)
    - aspiration pneumonitis
    - other: Addisonian crisis, thyroid storm, transfusion reaction
  - POD #3-7 (subacute): infections more likely
    - UTI, surgical site infection, IV site/line infection, septic thrombophlebitis, leakage at bowel anastomosis (tachycardia, hypotension, oliguria, abdominal pain)
  - POD #8+ (delayed)
    - intra-abdominal abscess, DVT/PE (can be anytime post-operative, most commonly POD #8-10), drug fever
    - other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, C. difficile colitis, endocarditis, sinusitis (from nasogastric tube)

Treatment

- treat primary cause
- antipyrexia (e.g. acetaminophen)

WOUND CARE (see Plastic Surgery, PL8)

- can shower POD #2-3 (epithelialization of wound occurs within 48 h)
- dressings can generally be removed POD #2 and left uncovered if dry (check with attending to be sure)
- examine wound if wet dressing, signs of infection (fever, tachycardia, pain)
- skin sutures and staples can be removed POD #7-10
  - exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, immunosuppressed) removed POD #14, earlier if signs of infection
- negative pressure dressings consist of foam and suction, promote granulation
  - ideal for large (grafted sites) or non-healing wounds (irradiated skin, ulcer)

DRAINS

- sometimes placed intraoperatively to prevent fluid accumulation (blood, pus, serum, bile, urine)
- can be used to assess quantity of third space fluid accumulation post-operatively
- potential route of infection, bring out through separate incision (vs. operative wound) to decrease risk of wound infection and remove as soon as possible
• types of drains
  - open (e.g. Penrose), higher risk of infection
  - closed: 1) Gravity drainage (e.g. Foley catheter); 2) Underwater-seal drainage system (e.g. chest tube); 3) Suction drainage (e.g. Jackson-Pratt)
  - sump (e.g. NGT)
• monitor drain outputs daily
• drains should be removed once drainage is minimal (<30-50 cc/24 h)
• evidence does not support routine post-operative drainage of abdominal cavity
• drains do not guarantee that the patient will not form a collection of fluid
• ridged drains can erode through internal structures, and excessive suction can cause necrosis

SURGICAL SITE INFECTION

Etiology
• S. aureus, E. coli, Enterococcus, Streptococcus spp., Clostridium spp.

Risk Factors

Table 4. Procedures and Their Impact on Surgical Site Infection

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clean</th>
<th>Clean-Contaminated</th>
<th>Contaminated</th>
<th>Dirty/Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Incision under sterile conditions; nontraumatic; no entrance of hollow organ</td>
<td>Incision under sterile conditions; ENTRANCE of hollow viscus; no evidence of active infection; minimal contamination</td>
<td>Incision under sterile conditions; MAJOR contamination of wound during procedure (i.e. gross spillage of stool, infection in biliary, respiratory, or GU systems)</td>
<td>Established infection present before wound is made in skin</td>
</tr>
<tr>
<td>Example</td>
<td>Wound created to repair hernia</td>
<td>Routine cholecystectomy; colon resection</td>
<td>Bowel obstruction with enterotomy and spillage of contents; necrotic bowel resection; fresh traumatic wounds</td>
<td>Appendiceal abscess; traumatic wound with contaminated devitalized tissue; perforated viscus</td>
</tr>
<tr>
<td>Infection Rate</td>
<td>&lt;2%</td>
<td>3-4%</td>
<td>7-10%</td>
<td>30-40%</td>
</tr>
<tr>
<td>Wound Closure</td>
<td>Primary closure</td>
<td>Primary closure</td>
<td>Often secondary closure</td>
<td>Secondary closure</td>
</tr>
</tbody>
</table>

• patient characteristics
  - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, chemotherapy
  - other factors
    - prolonged pre-operative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts), skin preparation, hypoxemia, hypothermia

Clinical Presentation
• typically fever POD #5-8 (Streptococcus and Clostridium can present in 24 h)
• pain, blanchable wound erythema, induration, purulent discharge, warmth
• complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, hernia

Prophylaxis
• used to reduce the chance of surgical site infections
  - pre-operative antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamycin)
    - within 1 h pre-incision; can re-dose at 1-2 half-lives (~q4-8h) in the OR
    - not required for low risk elective cholecystectomy, hemorrhoidectomy, fistulotomy, sphincterotomy for fissure
    - generally no need to continue prophylactic antibiotics post-operatively
    - reserve post-operative antibiotics for treatment of suspected or documented intra-abdominal infection
  - normothermia (maintain patient temperature 96.8-100.4ºF during OR)
  - hyperoxegenation (consider FiO2 of 80% in OR)
  - chlorhexidine-alcohol wash of surgical site
  - hair removal should not be performed unless necessary; if so, clipping superior to shaving
  - protect skin edges (moistened lap pads); consider delayed primary closure of incision for contaminated wounds

Treatment
• examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
• re-open affected part of incision, drain, pack, heal by secondary intention in most cases
• for deeper infections, debride necrotic and non-viable tissue
• antibiotics and demarcation of erythema only if cellulitis or immunodeficiency
WOUND HEMORRHAGE/HEMATOMA
- secondary to inadequate surgical control of hemostasis

Risk Factors
- anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial HTN, severe cough
- more common with transverse incisions through muscle

Clinical Features
- pain, swelling, discoloration of wound edges, leakage
- rapidly expanding neck hematoma can compromise airway and is a surgical emergency (consider opening wound at bedside)

Treatment
- pressure dressing
- open drainage ± wound packing (large hematoma only)
- if significant bleeding, may need to re-operate to find source (often do not find a discrete vessel)

SEROMA
- fluid collection other than pus or blood
- secondary to transection of lymph vessels
- delays healing
- increased infection risk

Treatment
- pressure dressing ± needle drainage
- if significant may need to re-operate

WOUND DEHISCENCE
- disruption of fascial layer, abdominal contents contained by skin only
- 95% caused by intact suture tearing through fascia

Clinical Features
- typically POD #1-3; most common presentation sign is serosanguinous or salmon-colored drainage from wound ± evisceration
- palpation of wound edge: should normally feel a “healing ridge” from abdominal wall closure (raised area of tissue under incision)

Risk Factors
- local: technical failure of closure, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, patient not fully paralyzed while closing, transverse incision
- systemic: smoking, malnutrition (hypalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, other (e.g. age, sepsis, uremia)
- DM alone is not a risk factor

Treatment
- place moist dressing over wound with binder around abdomen and transfer to OR
- may consider conservative management with debridement of fascial and/or skin margins

EVISCERATION
- protrusion of abdominal viscera through the abdominal wall
- also known as ‘burst abdomen’, is a surgical emergency (mortality rates as high as 45%)

Treatment
- take patient for operative closure, use slowly absorbable suture ± retention sutures

Urinary and Renal Complications

URINARY RETENTION
- may occur after any operation with general anesthesia or spinal anesthesia
- more likely in older males with history of benign prostatic hyperplasia, patients on anticholinergics

Clinical Presentation
- abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL
Treatment
• Foley catheter to rest bladder, then trial of voiding

OLIGURIA/ANURIA (see Nephrology, NP33)

Etiology
• prerenal vs. renal vs. postrenal
  ▪ most common post-operative cause is prerenal ± ischemic ATN
  ▪ external fluid loss: hemorrhage, dehydration, diarrhea
  ▪ internal fluid loss: third-spacing due to bowel obstruction, pancreatitis

Clinical Presentation
• urine output <0.5 cc/kg/h, increasing Cr, increasing BUN

Treatment
• according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

Post-Operative Dyspnea

• see Respiratory Complications below and Cardiac Complications, GS11

Etiology
• respiratory: atelectasis, pneumonia, pulmonary embolus (PE), ARDS, asthma, pleural effusion
• cardiac: MI, arrhythmia, CHF
• inadequate pain control

Respiratory Complications

ATELECTASIS
• comprises 90% of post-operative pulmonary complications

Clinical Features
• low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, tachypnea

Risk Factors
• COPD, smoking, obesity, elderly persons
• upper abdominal/thoracic surgery, oversedation, significant post-operative pain, poor inspiratory effort

Treatment
• pre-operative prophylaxis
  ▪ smoking cessation (best if >8 wk pre-operative)
  ▪ provide incentive spirometer and instruct how to use
• post-operative prophylaxis
  ▪ incentive spirometry, deep breathing exercise, chest physiotherapy, intermittent positive-pressure breathing
  ▪ selective NGT decompression after abdominal surgery
  ▪ short-acting neuromuscular blocking agents
  ▪ minimize use of respiratory depressive drug, good pain control, early ambulation

PNEUMONIA/PNEUMONITIS
• may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

Risk Factors
• aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NGT, pregnancy, seizure disorder
• non-aspiration: atelectasis, immobility, pre-existing respiratory disease

Clinical Features
• productive cough, fever
• tachycardia, cyanosis, respiratory failure, decreased LOC
• CXR: pulmonary infiltrate

Treatment
• prophylaxis: see atelectasis prophylaxis, pre-operative NPO/NGT, rapid sequence anesthetic induction
• immediate removal of debris and fluid from airway
• consider endotracheal intubation and flexible bronchoscopic aspiration
• IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. ceftriaxone, metronidazole)
PULMONARY EMBOLUS (see Respirology, R18)

Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset shortness of breath, tachycardia, fever
- most commonly POD #8-10, but can occur anytime post-operatively

Treatment
- IV heparin, long-term warfarin (INR = 2-3) for 3 mo
- Greenfield (IVC) filter if contraindications to anticoagulation or develops a complication while on anticoagulation
- prophylaxis: subcutaneous heparin (5,000 U bid) or LMWH, compression stockings (TED™ Hose)

PULMONARY EDEMA

Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anesthesia

Clinical Features
- shortness of breath, crackles at lung bases, CXR abnormal

Treatment (LMNOP)
- Lasix
- Morphine (decreases symptoms of dyspnea, venodilator and afterload reduction)
- Nitrates (venodilator)
- Oxygen + non-invasive ventilation
- Position (sit patient up)

RESPIRATORY FAILURE

Clinical Features
- dyspnea, cyanosis, evidence of obstructive lung disease
- earliest manifestations – tachypnea and hypoxemia (RR >25, pO2 <60)
- pulmonary edema, unexplained decrease in SaO2

Treatment
- ABCs, O2, ± intubation
- bronchodilators, diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO2 >60, consider ARDS

Cardiac Complications

- abnormal ECGs common in post-operative period (compare to pre-operative ECG)
- common arrhythmias: supraventricular tachycardia, atrial fibrillation (secondary to fluid overload, PE, MI)

MYOCARDIAL INFARCTION

- see Cardiology and Cardiac Surgery, C27
- surgery increases risk of MI
  - incidence
  - 0.5% in previously asymptomatic men >50 yr old
  - 40-fold increase in men >50 yr old with previous MI

Risk Factors
- pre-operative HTN, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intraoperative hypotension
- operations >3 h
- angina

Clinical Features
- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, hypotension
Intra-Abdominal Abscess

Definition
• collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

Etiology
• usually polymicrobial: Gram-negative bacteria, anaerobes
  • consider Gram-positives if coexisting cellulitis

Risk Factors
• emergency, contaminated OR
• GI surgery with anastomoses
• risk factors for poor healing (DM, poor nutrition, etc.)
• may occur POD #3 after laparotomy when third space fluid re-distribution occurs

Clinical Features
• persistent spiking fever, dull pain, weight loss
• mass difficult to palpate
• peritoneal signs if abscess perforation and secondary peritonitis
• leukocytosis or leukopenia (immunocompromised, elderly)
• co-existing effusion (pleural effusion with subphrenic abscess)
• common sites: pelvis, Morrison’s pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, psoas

Investigations
• CBC, blood cultures x2
• CT ± water-soluble contrast
• DRE (pelvic abscess)

Treatment
• eradication (preferred), laparoscopy, open drainage
• subsequent antibiotic coverage, ciprofloxacin (Cipro®) + metronidazole (Flagyl®)

Paralytic Ileus
• see Bowel Obstruction, GS24

Delirium
• see Psychiatry, PS16 and Neurology, N19

Thoracic Surgery

Hiatus Hernia

Figure 6. Types of hiatus hernia
SLIDING HIATUS HERNIA (Type I)

- see Figure 6
- herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

Risk Factors
- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, heavy lifting)
- smoking

Clinical Features
- majority are asymptomatic
- larger hernias frequently associated with GERD (60-80%) due to decreased competence of the LES

Complications
- most common complication is GERD
- other complications are rare and are related to reflux
  - esophagitis (dysphagia, heartburn)
  - consequences of esophagitis (peptic stricture, Barrett’s esophagus, esophageal carcinoma)
  - extra-esophageal complications (pneumonitis/pneumonia, asthma, cough, laryngitis)

Investigations
- CXR, barium swallow, endoscopy, or esophageal manometry (technique for measuring LES pressure)
- 24-48 h esophageal pH monitoring to quantify reflux
- gastroscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett’s esophagus, and cancer

Treatment
- lifestyle modification
  - stop smoking, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint, and fat
  - medical
    - antacid, H₂-antagonist, PPI, prokinetic agent
  - surgical (<15%)
    - if failure of medical therapy, esophageal stricture, severe nocturnal aspiration, Barrett’s esophagus
    - anti-reflux procedure (usually laparoscopic) e.g. Nissen fundoplication
      - fundus of stomach is wrapped around the lower esophagus and sutured in place
      - 90% success rate at experienced centers

PARAESOPHAGEAL HIATUS HERNIA (Type II)

- see Figure 6
- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
- least common esophageal hernia (<10%)

Clinical Features
- usually asymptomatic due to normal GE junction
- pressure sensation in lower chest, dysphagia

Complications
- hemorrhage, incarceration, strangulation (gastric volvulus), obstruction, gastric stasis ulcer (Cameron lesions – causes Fe-deficiency anemia)

Treatment
- surgery to prevent severe complications
  - reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
  - may consider suturing stomach to anterior abdominal wall (gastropyexy)
  - in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy)

MIXED HIATUS HERNIA (Type III)

- see Figure 6
- combination of Types I and II

TYPE IV HERNIA
- herniation of other abdominal organs into thorax: colon, spleen, small bowel
Esophageal Perforation

**Etiology**
- iatrogenic (most common)
  - endoscopic, dilatation, biopsy, intubation, operative, NGT placement
  - barogenic
    - trauma
    - repeated, forceful vomiting (Boerhaave’s syndrome)
    - other: convulsions, defecation, labor (rare)
  - ingestion injury
    - foreign body, corrosive substance
  - carcinoma

**Clinical Features**
- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, respiratory compromise
- subcutaneous emphysema, pneumothorax, hematemesis

**Investigations**
- CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air
- CT chest: widened mediastinum, pneumomediastinum
- contrast swallow (water-soluble then thin barium): contrast extravasation

**Treatment**
- supportive if rupture is contained
  - NPO, vigorous fluid resuscitation, broad-spectrum antibiotics, possible percutaneous drainage
- surgical
  - <24 h
    - primary closure of a healthy esophagus or resection of diseased esophagus
  - >24 h or non-viable wound edges
    - diversion and exclusion followed by delayed reconstruction (i.e. cervical esophagostomy (“spit fistula”) proximally, close esophagus distally, gastrostomy/jejunostomy tube for decompression/feeding)

**Complications**
- sepsis, abscess, fistula, empyema, mediastinitis, death
- post-operative esophageal leak
- mortality 10-50% dependent on timing of diagnosis

Esophageal Carcinoma

**Epidemiology**
- M:F = 3:1
- onset 50-60 yr of age
- upper (20-33%), middle (33%), lower (33-50%)
- main types:
  - most common worldwide: SCC in upper 2/3 of esophagus
  - most common in Western countries: adenocarcinoma in distal 1/3 of esophagus

**Risk Factors**
- geographic variation in incidence
- SCC
  - underlying esophageal disease such as strictures, diverticula, achalasia
  - smoking, alcohol, hot liquids, pickled foods (high in nitrosamines)
  - more common in patients from Asia
- adenocarcinoma
  - Barrett’s esophagus (most important), smoking, obesity (increased reflux), GERD

**Clinical Features**
- frequently asymptomatic; late presentation
- progressive dysphagia (mechanical): first solids then liquids
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis, anemia
- tracheoesophageal or bronchoesophageal fistula
- direct, hematogenous, or lymphatic spread
  - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aorta, pericardium, liver, lung, bone, celiac, and mediastinal nodes

**Perioperative Chemo(radio)therapy vs. Primary Surgery for Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction, and Lower Esophagus**

**Study**: Review of RCTs to examine the effect of perioperative chemotherapy for gastroesophageal adenocarcinoma on survival and other clinically relevant outcomes.

**Results/Conclusions**: 14 RCTs, 2,422 participants.

1. Perioperative chemotherapy was associated with a significantly longer overall survival (HR 0.81, 95% CI 0.73-0.89), a relative survival increase of 19% and an absolute increase of 9%.
2. Tumors of the GE junction showed a more pronounced response to perioperative chemotherapy compared to other sites.
3. Combined chemoradiotherapy was more effective for tumors of the esophagus and GE junction compared to chemotherapy alone.
4. Perioperative chemotherapy was more effective in younger patients and is associated with longer disease-free survival, higher rates of R0 resection, and a more favorable tumor stage upon resection.
5. Resection with negative margins is a strong predictor of survival.
Investigations
- barium swallow: shows narrowing – suggestive but not diagnostic
- esophagoscopy: biopsy and assess resectability
- endoscopic ultrasound (EUS)
  - visualize local disease
  - regional nodal involvement (most accurate way to stage the cancer) ± FNA
- bronchoscopy ± thoracoscopy
  - rule out airway invasion in tumors of the upper and mid esophagus
- full metastatic workup (CT head, CT chest/abdomen/pelvis, LFTs, etc.)

Treatment
- if present with distant metastatic disease
  - treat with systemic therapy and palliate symptoms (esophageal stent)
- if locally advanced (locally invasive disease or nodal disease on CT or EUS)
  - multimodal therapy
    - concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
    - possibility of curative esophagectomy after chemoradiation if disease responds well
    - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if early stage (non-transmural and without evidence of nodal disease)
  - esophagectomy (transhiatal or trans-thoracic approach) and lymphadenectomy
  - anastomosis in chest or neck
  - stomach most often used for reconstruction; may also use colon
  - neoadjuvant chemotherapy and radiation are controversial
  - adjuvant chemotherapy ± radiation usually recommended for post-operative node-positive disease
- more advanced stages
  - neoadjuvant chemotherapy ± radiation followed by esophagectomy

Prognosis
- prognosis usually poor because presentation is usually at advanced stage (5 yr survival for all stages is only 17%)

OTHER DISORDERS
- esophageal varices (see Gastroenterology, G26)
- Mallory-Weiss tear (see Gastroenterology, G27)

Pleur, Lung, and Mediastinum
- see Respirology, R22

Tube Thoracostomy

Indications
- to drain abnormal large-volume air or fluid collections in the pleural space
  - pleural effusion, hemothorax, chylothorax, empyema
  - pneumothorax, if
    - large or progressive
    - patient is on mechanical ventilation
    - bronchopleural fistula
    - tension pneumothorax
- to treat symptomatic and/or recurrent pleural effusion
  - see Respirology, R24
  - for long-term drainage of malignant effusions
  - via facilitation of pleurodesis (obliteration of the pleural space by instilling talc or doxycycline to cause fibrosis and adherence of parietal and visceral pleura)

Complications
- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators:
  - tubes may dissect along the external chest wall, or may be placed below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma
- risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0-1.5 L)

Figure 7. Typical thoracic surgery incisions

Figure 8. Tube thoracostomy
Lung Transplantation

Conditions Leading to Transplantation
- chronic acquired lung disease: COPD
- genetic: CF, emphysema due to α-1 antitrypsin deficiency
- idiopathic interstitial pneumonias: IPF, nonspecific interstitial pneumonitis
- HTN-related: IPAH, secondary pulmonary HTN, Eisenmenger’s syndrome
- other: sarcoidosis, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis

Clinical Indications
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and limited expected survival over the next 2 yr

Criteria for Transplantation
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

Contraindications
- uncontrolled or untreatable pulmonary or extrapulmonary infection
- malignancy in the last 2 yr
- advanced cardiopulmonary disease
- significant chest wall/spinal deformity
- active cigarette smoking
- HIV infection, ongoing HBV or HCV infections

Post-Operative Complications
- primary graft dysfunction: main cause is ischemia-reperfusion injury, graded by PaO2/FiO2 ratio and CXR findings
- airway anastomotic complications (focal infection, bronchial necrosis and dehiscence, excess granulation tissue, tracheobronchomalacia, stenosis, fistula)
- chronic graft dysfunction: bronchiolitis obliterans syndrome
- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disease, colon, breast, Kaposi’s sarcoma, bladder)

Prognosis
- median survival for all adult recipients: 5.4 yr
- 1 yr survival: COPD > IPF > IPAH
- 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD, IPF

Chronic Obstructive Pulmonary Disease

- see Respirology, R9

Treatment
- indications for surgical management
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation
- contraindications
  - age >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - diffusing capacity of lung for carbon monoxide <20% of predicted, PaCO2 >60 mmHg, PaO2 <45 mmHg
- surgical procedures
  - lung volume reduction surgery: wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS

Complications of Treatment
- air leak: may require reintubation and mechanical ventilation
- arrhythmias, pneumonia

Prognosis
- total mortality at 2 yr same as with maximal medical therapy, but better exercise capacity and quality of life with LVRS

Long-Term Survival Analysis of the Canadian Lung Volume Reduction Surgery Trial
Study: Retrospective observational study assessing the long-term survival of patients enrolled in the CLVRS at 8-10 yr follow-up.
Results/Conclusions: 62 patients total. 52 patients had a median survival time of 4.11 yr. Compared with the best medical care group, patients in the LVRS group showed a 16 mo survival advantage and a 20% reduction in mortality. LVRS may provide long-term benefits in the treatment of end-stage emphysema, however, the results were not statistically significant.
Peptic Ulcer Disease

GASTRIC ULCERS
- see Gastroenterology, G12

Indications for Surgery
- unresponsive to medical treatment (intractability)
  ▪ always operate if fails to heal completely, even if biopsy negative: could be primary gastric lymphoma or adenocarcinoma
- dysplasia or carcinoma
  ▪ always biopsy ulcer for malignancy
- hemorrhage: 3x greater risk of bleeding compared to duodenal ulcers
- complications: obstruction, perforation, bleeding
- surgical treatment is increasingly rare due to H. pylori eradication and medical treatment

Procedures
- distal gastrectomy with ulcer excision: Billroth I or Billroth II
- vagotomy and pyloroplasty only if acid hypersecretion (rare)
- wedge resection if possible or biopsy with primary repair

DUODENAL ULCERS
- see Gastroenterology, Bleeding Peptic Ulcer, G13, and Peptic Ulcer Disease, G12
- most within 2 cm of pylorus (duodenal bulb)

Indications for Surgery
- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
  ▪ decision to operate based on amount of blood loss (usually >8 units), rate of bleeding, and hemodynamic stability
- intractable despite medical management (endoscopy)

Procedures
- Graham patch of perforated ulcer-plication of ulcer and omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- pyloroplasty, gastroduodenostomy, or gastrojejunostomy (improved drainage)
- antrectomy (eliminate hormonal stimulation from the antrum)
- gastric resection (decrease the number of parietal cells)
- vagotomy
  ▪ rarely done now due to H. pylori eradication and PPI

Complications of Surgery
- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, afferent loop syndrome (see Complications of Gastric Surgery, GS20)
### Table 5. Complications of Duodenal Ulceration

<table>
<thead>
<tr>
<th>Complication</th>
<th>Clinical Features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perforated Ulcer</strong></td>
<td>Sudden onset of pain (possibly in RLO due to track down right paracolic gutter)</td>
<td>Investigation: CXR – free air under diaphragm (70% of patients)</td>
</tr>
<tr>
<td></td>
<td>Acute abdomen: rigid, diffuse guarding</td>
<td>Treatment: Oversew ulcer (plication) and omental (Graham) patch – most common treatment</td>
</tr>
<tr>
<td></td>
<td>Initial chemical peritonitis followed by bacterial peritonitis</td>
<td></td>
</tr>
<tr>
<td><strong>Posterior Penetration</strong></td>
<td>Elevated amylase/lipase if penetration into pancreas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Constant mid-epigastric pain burrowing into back, unrelated to meals</td>
<td></td>
</tr>
<tr>
<td><strong>Hemorrhage</strong></td>
<td>Gastroduodenal artery involvement</td>
<td>Resuscitation initially with crystalloids; blood transfusion if necessary</td>
</tr>
<tr>
<td></td>
<td>Ulcer can lead to edema, fibrosis of pyloric channel, neoplasm</td>
<td>Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope</td>
</tr>
<tr>
<td></td>
<td>N/V (undigested food, non-bilious), dilated stomach, crampy abdominal pain</td>
<td>Consider interventional radiology: angiography with embolization/coiling</td>
</tr>
<tr>
<td></td>
<td>Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken)</td>
<td>Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty</td>
</tr>
<tr>
<td><strong>Gastric Outlet Obstruction</strong></td>
<td>NGT decompression and correction of hypochloremic, hypokalemic metabolic alkalesis</td>
<td></td>
</tr>
</tbody>
</table>

### Gastric Carcinoma

#### Epidemiology
- **M:F = 3:2**
- incidence of adenocarcinoma < 10 (US) vs. 60 (Japan, Korea) per 100,000 (incidence highest in Asia and Latin America)
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr

#### Risk Factors
- *H. pylori*, causing chronic atrophic gastritis
- hereditary nonpolyposis colorectal cancer (HNPCC), hereditary diffuse gastric carcinoma (HDGC)
- smoking, alcohol, smoked food, nitrosamines
- pernicious anemia associated with achlorhydria and chronic atrophic gastritis
- gastric adenomatous polyps
- previous partial gastrectomy (>10 yr post-gastrectomy)
- hypertrophic gastropathy
- blood type A

#### Clinical Features
- clinical suspicion
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
  - asymptomatic, insidious, or late onset of symptoms
  - postprandial abdominal fullness, vague epigastric pain
  - anorexia, weight loss
  - burping, N/V, dyspepsia, dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, iron-deficiency anemia
- metastasis:
  - peritoneum, liver, lung, brain

#### Investigations
- OGD and biopsy; EUS to assess pre-operative T-stage and N-stage
- CT chest/abdomen/pelvis CT (for metastatic workup see Table 7)
Table 6. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>NX</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>N0</td>
</tr>
<tr>
<td>T1a</td>
<td>Invasion into lamina propria or muscularis mucosae</td>
<td>N1 Metastasis in 1-2 regional nodes</td>
</tr>
<tr>
<td>T1b</td>
<td>Invasion into submucosa</td>
<td>N2 Metastasis in 3-6 regional nodes</td>
</tr>
<tr>
<td>T2</td>
<td>Invasion into muscularis propria</td>
<td>N2a Metastasis in 7-15 regional nodes</td>
</tr>
<tr>
<td>T3</td>
<td>Penetration of subserosal connective tissue without tissue invasion of visceral peritoneum or adjacent structures</td>
<td>N2b Metastasis in ≥16 regional nodes</td>
</tr>
<tr>
<td>T4a</td>
<td>Invasion into serosa</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Invasion into adjacent structures</td>
<td></td>
</tr>
</tbody>
</table>

Treatment
- adenocarcinoma
  - proximal lesions
    - total gastrectomy and Roux-en-Y esophagojejunostomy
  - distal lesions
    - distal gastrectomy or subtotal gastrectomy: wide (5-6 cm) margins, en bloc removal of omentum and lymph nodes
- palliation
  - gastric resection to decrease bleeding and relieve obstruction, enables the patient to eat
  - radiation therapy
  - studies are showing larger role for chemotherapy

Gastrointestinal Stromal Tumor

Epidemiology
- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach's plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- often discovered incidentally on CT, laparotomy, or endoscopy

Risk Factors
- Carney's triad: GISTs, paraganglioma, and pulmonary chondroma
- Type IA neurofibromatosis

Investigations
- EUS is helpful
- pre-operative biopsy: controversial, but useful for indeterminate lesions:
  - not recommended if index of suspicion for GIST is high
  - percutaneous biopsy is NOT recommended due to high friability and risk of peritoneal spread

Treatment
- surgical resection if >2 cm; follow with serial endoscopy if <2 cm and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT recommended, as GISTs rarely metastasize to lymph nodes
  - consider imatinib post-operative for high-risk GIST (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - chemotherapy with imatinib
Prognosis
• risk of metastatic potential depends on
  ▪ tumor size (worse if >10 cm)
  ▪ mitotic activity (worse if >5 mitotic figures or 50/hpf)
  ▪ degree of nuclear pleomorphism
  ▪ location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
• metastases to liver, omentum, peritoneum; nodal metastases rare

Bariatric Surgery
• weight reduction surgery for morbid obesity
• indications: BMI >40 or BMI >35 with related comorbidity (e.g. DM, CAD, sleep apnea, HTN, severe joint disease)
• requires multidisciplinary evaluation and follow-up

Surgical Options
• malabsorptive/restrictive
  ▪ laparoscopic Roux-en-Y gastric bypass (most common – see Figure 9)
  ▪ staple off small gastric pouch (restrictive) with Roux-en-Y limb to pouch (malabsorptive) with dumping syndrome physiology
  ▪ most effective, higher complication rates
• restrictive
  ▪ laparoscopic adjustable gastric banding
    ▪ silicone band around fundus creates pouch, adjustable through port under skin
  ▪ laparoscopic sleeve gastrectomy
    ▪ resects most of the greater curvature (about 75% of the stomach); becoming popular weight-loss procedure
• malabsorptive
  ▪ biliopancreatic diversion with duodenal switch
  ▪ gastrectomy, enteroenterostomy, duodenal division closure and duodenoenterostomy

Complications
• perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
• obstruction at enteroenterostomy (see Complications of Gastric Surgery, below)
• staple line dehiscence
• internal hernias
• dumping syndrome
• cholelithiasis due to rapid weight loss (20-30%)
• band abscess (if long-term)

Complications of Gastric Surgery
• most resolve within 1 yr

Alkaline Reflux Gastritis (see Figure 10A)
• duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
• treatment
  ▪ medical: H₂-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  ▪ surgical: conversion of Billroth I or II to Roux-en-Y

Afferent Loop Syndrome (see Figure 10B)
• accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
• clinical features
  ▪ early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
• treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Dumping Syndrome (see Figure 10C)
• early (~15 min post-prandial)
  ▪ etiology
    ▪ hyperosmotic chyme released into small bowel (fluid accumulation and jejunal distention)
  ▪ clinical features
    ▪ post-prandial symptoms
    ▪ epigastric fullness or pain, emesis, nausea, diarrhea, palpitations, dizziness, tachycardia, diaphoresis
Blind-Loop Syndrome (see Figure 10D)
- bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
- clinical features
  - anemia/weakness, diarrhea, malnutrition, abdominal pain, and hypocalcemia
- treatment: broad-spectrum antibiotics, surgery (conversion to Billroth I)

Postvagotomy Diarrhea (see Figure 10E)
- up to 25%
- bile salts in colon inhibit water resorption
- treatment: medical (cholestyramine), surgical (reversed interposition jejunal segment)

Small Intestine

Tumors of Small Intestine

BENIGN TUMORS
- 10x more common than malignant
- usually asymptomatic until large
- most common sites: terminal ileum, proximal jejunum
- polyps
  - adenomas
  - hamartomas
  - FAP (see Familial Colon Cancer Syndromes, GS33)
- juvenile polyps
- other: leiomyomas, lipomas, hemangiomas

Table 7. Malignant Tumors of the Small Intestine

<table>
<thead>
<tr>
<th>Epidemiology</th>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Lymphoma</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased incidence 50-60 yr</td>
<td>N/V, anemia, GI bleeding, jaundice, weight loss (less common)</td>
<td></td>
<td>Highest incidence in 70s M&gt;F</td>
<td>Most common site of GI metastases in patients with metastatic melanoma</td>
</tr>
<tr>
<td>Usually 50-70 yr M&gt;F</td>
<td>Early metastasis to lymph nodes</td>
<td>Usually asymptomatic, incidental finding</td>
<td>Usually non-Hodgkin’s lymphoma</td>
<td></td>
</tr>
<tr>
<td>90% metastatic at time of operation</td>
<td>Carcinoid syndrome (&lt;10%)</td>
<td>Carcinoid, celiac disease, autoimmune disease, immunosuppression, radiation therapy, nodular lymphoid hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain (common)</td>
<td>N/V, anemia, GI bleeding, jaundice, weight loss (less common)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features

<table>
<thead>
<tr>
<th>Investigations</th>
<th>N/V, anemia, GI bleeding, jaundice, weight loss (less common)</th>
<th>N/V, anemia, GI bleeding, jaundice, weight loss (less common)</th>
<th>N/V, anemia, GI bleeding, jaundice, weight loss (less common)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT abdomen/pelvis</td>
<td>Most found incidentally at surgery for obstruction or appendectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Chest thorax/abdomen/pelvis</td>
<td>Consider small bowel enteroclysis to look for primary</td>
<td>Consider small bowel enteroclysis to look for primary</td>
</tr>
<tr>
<td></td>
<td>Elevation incidental Carcinoid (breakdown product of serotonin) in urine</td>
<td>incidental Carcinoid (breakdown product of serotonin) in urine</td>
<td>incidental Carcinoid (breakdown product of serotonin) in urine</td>
</tr>
<tr>
<td></td>
<td>or increased 5-HT in blood</td>
<td>Retrospectively identify lesion secretes serotonin, kinins, and vasoactive peptides directly</td>
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</tr>
<tr>
<td></td>
<td>Retrospectively identify lesion secretes serotonin, kinins, and vasoactive peptides directly</td>
<td>to systemic circulation (normally inactivated by liver)</td>
<td>to systemic circulation (normally inactivated by liver)</td>
</tr>
<tr>
<td></td>
<td>Requires liver involvement: lesion secretes serotonin, kinins, and vasoactive peptides directly to systemic circulation (normally inactivated by liver)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obstruction and bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Carcinoid Syndrome Symptoms – FDR
- Flushing
- Diarrhea
- Right-sided heart failure
Abdominal Hernia

**Definition**
- defect in abdominal wall causing abnormal protrusion of intra-abdominal contents

**Epidemiology**
- M:F = 9:1
- lifetime risk of developing a hernia: males 20-25%, females 2%
- frequency of occurrence: 50% indirect inguinal, 25% direct inguinal, 8-10% incisional (ventral), 5% femoral, 3-8% umbilical
- most common surgical disease of males

**Risk Factors**
- activities which increase intra-abdominal pressure
  - obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, heavy lifting
- congenital abnormality (e.g. patent processus vaginalis, indirect inguinal hernia)
- previous hernia repair, especially if complicated by wound infection
- loss of tissue strength and elasticity (e.g. hiatus hernia, aging, repetitive stress)

**Clinical Features**
- mass of variable size
- tenderness worse at end of day, relieved with supine position or with reduction
- abdominal fullness, vomiting, constipation
- transmits palpable impulse with coughing or straining

**Investigations**
- physical examination usually sufficient
- ultrasound ± CT (CT required for obturator hernias, internal abdominal hernias and Spigelian and/or femoral hernias in obese patients)

**Classification**
- complete: hernia sac and contents protrude through defect
- incomplete: partial protrusion through the defect
- internal hernia: sac herniating into or involving intra-abdominal structure
- external hernia: sac protrudes completely through abdominal wall
- strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  - requires emergency repair
- incarcerated hernia: irreducible hernia, not necessarily strangulated
- Richter’s hernia: only part of bowel circumference (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
  - a strangulated Richter’s hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation in the absence of obstructive symptoms
- sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)

**Anatomical Types**
- groin
  - indirect and direct inguinal, femoral (see Figure 13)
  - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastrium: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Litter’s (involving Meckel’s), Amyand’s (containing appendix), lumbar, obturator, peristomal, umbilical, Spigelian (ventral hernia through linea semilunaris), Grynfeltt-Lesshaft hernia (superior lumbar hernia), Petit’s hernia (inferior lumbar triangle)
Combinations
• incarceration
• strangulation
  ▪ small, new hernias more likely to strangulate
  ▪ femoral >> indirect inguinal > direct inguinal
  ▪ intense pain followed by tenderness
  ▪ intestinal obstruction, gangrenous bowel, sepsis
  ▪ surgical emergency
• DO NOT attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous
  ▪ will cause closed loop SBO – and EMERGENCY

Treatment
• surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for
  symptomatic relief, for cosmesis, if asymptomatic can delay surgery
• repair may be done open or laparoscopic and may use mesh for tension-free closure
• most repairs are now done using tension-free techniques – a plug in the hernial defect and a
  patch over it or patch alone
• observation is acceptable for small asymptomatic inguinal hernias

Post-Operative Complications
• recurrence (15-20%)
  ▪ risk factors: recurrent hernia, age >50, smoking, BMI >25, poor pre-operative functional status
    (ASA ≥3 – see Anesthesia, A3), associated medical conditions: type 2 DM, hyperlipidemia,
    immunosuppression, any comorbid conditions increasing intra-abdominal pressure
  ▪ less common with mesh/”tension-free” repair
• scrotal hematoma (3%)
• painful scrotal swelling from compromised venous return of testes
• deep bleeding: may enter retroperitoneal space and not be initially apparent
• difficulty voiding
• nerve entrapment
  ▪ ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  ▪ genital branch of genitofemoral (in spermatic cord)
• stenosis/occlusion of femoral vein
• acute leg swelling
• painful scrotal swelling from compromised venous return of testes
• groin pain following surgical repair
• acute leg swelling

Groin Hernias

Table 8. Groin Hernias

<table>
<thead>
<tr>
<th>Hernia Type</th>
<th>Direct Inguinal</th>
<th>Indirect Inguinal</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>1% of all men</td>
<td>Most common hernia in men and women</td>
<td>Affects mostly females</td>
</tr>
<tr>
<td>Etiology</td>
<td>Acquired weakness of transversalis fascia</td>
<td>Congenital persistence of processus vaginalis in 20% of adults</td>
<td>Pregnancy – weakness of pelvic floor musculature</td>
</tr>
<tr>
<td></td>
<td>“Wear and tear”</td>
<td>Increased intra-abdominal pressure</td>
<td>Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Through Hesselbach’s triangle</td>
<td>Originates in deep inguinal ring</td>
<td>Into femoral canal, below inguinal ligament but may override it</td>
</tr>
<tr>
<td></td>
<td>Medial to inferior epigastric artery</td>
<td>Lateral to inferior epigastric artery</td>
<td>Medial to femoral vein within femoral canal</td>
</tr>
<tr>
<td></td>
<td>Usually does not descend into scrotal sac</td>
<td>Often descends into scrotal sac (or labia majora)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgical repair</td>
<td>Surgical repair</td>
<td>Surgical repair</td>
</tr>
<tr>
<td>Prognosis</td>
<td>3-4% risk of recurrence</td>
<td>&gt;1% risk of recurrence</td>
<td></td>
</tr>
</tbody>
</table>

Table 9. Superficial Inguinal Ring vs. Deep Inguinal Ring*

<table>
<thead>
<tr>
<th>Hernia Type</th>
<th>Superficial Inguinal Ring</th>
<th>Deep Inguinal Ring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening</td>
<td>Opening in external abdominal aponeurosis, palpable superior and lateral to pubic tubercle</td>
<td>Opening in transversalis fascia: palpable superior to mid-inguinal ligament</td>
</tr>
<tr>
<td></td>
<td>Superior border: medial crus of external abdominal aponeurosis</td>
<td>Medial border: inferior epigastric vessels</td>
</tr>
<tr>
<td></td>
<td>Lateral border: lateral crus of external oblique aponeurosis</td>
<td>Superior-lateral border: internal oblique and transversus abdominis muscles</td>
</tr>
<tr>
<td>Roof</td>
<td>Intercrural fibers</td>
<td>Inferior border: inguinal ligament</td>
</tr>
</tbody>
</table>

*see Basic Anatomy Review, Figure 2, GS22

Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men: A Randomized Clinical Trial

JAMA 2019;321:292-292
Purpose: To compare pain and the physical component score (PCS) of the Short Form-36 Version 2 survey at 2 yr in men with minimally symptomatic inguinal hernias treated with watchful waiting or surgical repair.
Methods: 917 of 170 men (n=364 watchful waiting, n=553 surgical repair) followed up for 2-4.5 yr. Watchful-waiting patients were followed up at 6 mo and annually and watched for hernia symptoms; repair patients received standard open tension-free repair and were followed up at 3 and 6 mo and annually. The main outcome was pain and discomfort interfering with usual activities at 2 yr and change in PCS from baseline to 2 yr. Secondary outcomes were complications, patient-reported pain, functional status, activity levels, and satisfaction with care.
Results: Primary intention-to-treat outcomes were similar at 2 yr for watchful waiting vs. surgical repair: pain limiting activities (5.1% vs. 2.2%, respectively; p=0.06 [corrected]; PCS (improvement over baseline, 0.29 points vs. 0.13 points; p=0.79). Twenty-three percent of patients assigned to watchful waiting crossed over to receive surgical repair (increase in hernia-related pain was the most common reason offered; 17% assigned to receive repair crossed over to watchful waiting. Self-reported pain in watchful-waiting patients crossing over improved after repair. Occurrence of post-operative hernia-related complications was similar in patients who received repair vs assigned and in watchful-waiting patients who crossed over. One watchful-waiting patient (0.7%) experienced acute hernia incarceration without strangulation within 2 yr; a second had acute incarceration with bowel obstruction at 4 yr, with a frequency of 1.6/1,000 patient/yr inclusive of patients following up for as long as 4.5 yr.
Conclusion: Watchful waiting is an acceptable option for men with minimally symptomatic inguinal hernias. Delays surgical repair until symptoms increase is safe because acute hernia incarcerations occur rarely.
**Bowel Obstruction**

**Definition**
- partial or complete blockage of the bowel resulting in failure of intestinal contents to pass through lumen

**Pathogenesis**
- disruption of the normal flow of intestinal contents leading to proximal dilatation and distal decompression
- may take 12-24 h to decompress, therefore passage of feces and flatus may occur after the onset of obstruction
- bowel ischemia may occur if blood supply is strangulated or if bowel wall inflammation leads to venous congestion
- bowel wall edema and disruption of normal bowel absorptive function can lead to increased intraluminal fluid and transudative fluid loss into peritoneal cavity, electrolyte disturbances

**Risk Factors**
- prior abdominal or pelvic surgery, abdominal wall or groin hernia, history of malignancy, prior radiation

**Differential Diagnosis**
- SBO, ILBO, pseudo-obstruction

**Clinical Features**
- must differentiate between obstruction and ileus, and characterize obstruction as small vs. large bowel, acute vs. chronic, partial vs. complete (constipation vs. obstipation), strangulating vs. non-strangulating, and with vs. without perforation
- differentiation between small and large bowel obstruction is key as LBO is a surgical emergency and often requires early surgery to avoid perforation

**Table 10. Bowel Obstruction vs. Paralytic Ileus**

<table>
<thead>
<tr>
<th></th>
<th>SBO</th>
<th>LBO</th>
<th>Paralytic Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, Vomiting</td>
<td>Early, may be bilious</td>
<td>Late, may be feculent</td>
<td>Present</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Colicky</td>
<td>Colicky</td>
<td>Minimal or absent</td>
</tr>
<tr>
<td>Abdominal Distention</td>
<td>+ (prox SBO), ++ (distal SBO)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bowel Sounds</td>
<td>Normal, increased Absent if secondary ileus (delayed presentation)</td>
<td>Normal, increased (borborygmi) Absent if secondary ileus (delayed presentation)</td>
<td>Decreased, absent</td>
</tr>
<tr>
<td>AXR Findings</td>
<td>Air-fluid levels &quot;Ladder&quot; pattern (plicae circularis) Proximal distention (&gt;3 cm) + no colonic gas</td>
<td>Air-fluid levels &quot;Picture frame&quot; appearance Proximal distention + distal decompression No small bowel air if competent ileocecal valve Coffee bean sign (sigmoid volvulus)</td>
<td>Air throughout small bowel and colon</td>
</tr>
</tbody>
</table>

**Complications (of total obstruction)**
- strangulating obstruction (10% of bowel obstructions) = surgical emergency
  - cramping pain turns to continuous ache, hematemesis, melena (if infarction)
  - fever, leukocytosis, tachycardia
  - peritoneal signs, early shock
  - see Intestinal Ischemia, GS28
- other
  - perforation; secondary to ischemia and luminal distention
  - sepsisemia
  - hypovolemia (due to third spacing)

**Investigations**
- radiological
  - upright CXR or left lateral decubitus to rule out free air, usually seen under the right hemidiaphragm
  - abdominal x-ray (3 views) to determine SBO vs. LBO vs. ileus
    - if ischemic bowel look for: free air, pneumatoasis, thickened bowel wall, air in portal vein, dilated small and large bowels, thickened or hose-like haustra (normally finger-like projections)
other
- most used: CT provides information on level of obstruction, severity, cause
  - important to rule out closed loop obstruction, especially in the elderly
- less used: upper GI series/small bowel series for SBO (if no cause apparent, i.e. no hernias, no previous surgeries)
- if suspect LBO, consider a rectal water-soluble (Gastrografin® for PO/PR; Hypaque® for IV) enema rather than barium enema (can thicken and cause complete obstruction)
- may consider ultrasound or MRI in pregnant patients

• laboratory
  - may be normal early in disease course
  - BUN, creatinine, hematocrit to assess degree of dehydration
  - fluid, electrolyte abnormalities
  - amylase elevated
  - metabolic alkalosis due to frequent emesis
  - if strangulation: leukocytosis with left shift, lactic acidosis, elevated LDH (late signs)

Treatment
- stabilize vitals, fluid and electrolyte resuscitation
- NGT to relieve vomiting, prevent aspiration, and decompress small bowel by prevention of further distention by swallowed air
- Foley catheter to monitor ins/outs

### Small Bowel Obstruction

**Etiology**

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Intramural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intussusception</td>
<td>Crohn’s</td>
<td>Adhesions</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Radiation stricture</td>
<td>Incarcerated hernia</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma</td>
<td>Peritoneal carcinomatosis</td>
</tr>
</tbody>
</table>

**Treatment**
- consider whether complete or partial obstruction, ongoing or impending strangulation, location and cause
  - SBO with history of abdomen/pelvic surgery → conservative management (NGT decompression, GI rest, serial abdominal exams) → surgery if no resolution in 48-72 h or complications
  - complete SBO, strangulation → urgent surgery after stabilizing patient with fluid resuscitation
  - SBO with no previous surgery and no evidence of carcinomatosis → operate
  - trial of medical management may be indicated in Crohn’s, recurrent SBO, carcinomatosis
  - special case: early post-operative SBO (within 30 d of abdominal surgery) → prolonged trial of conservative therapy may be appropriate, surgery is reserved for complications such as strangulation

**Prognosis**
- mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%

### Large Bowel Obstruction

**Etiology**

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Intramural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Adenocarcinoma</td>
<td>Volvulus</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>IBD stricture</td>
<td>Adhesions</td>
</tr>
<tr>
<td>Radiation stricture</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 12. Common Causes of LBO**

- MUST DO
  - Rule out CRC in constipated patient
  - Send for TURP in patient with BPH (treat intra-abdominal HTN)

- Increased Risk of Perforation with Distention as seen on Abdomen Imaging
  - Small bowel ≥3 cm
  - Distal colon ≥6 cm
  - Proximal colon ≥9 cm
  - Cecum ≥12 cm

- Patients presenting with a SBO in setting of “virgin” abdomen should have surgery ASAP – EXCEPTION: malignant obstruction ASAP

- In a non-virgin abdomen – adhesional SBOs resolve spontaneously with NGT decompression 70% of time

- Top 3 Causes of SBO (in order)
  - ABC
    - Adhesions
    - Bulge (hernias)
    - Cancer (neoplasms)

- Causes of SBO
  - SHAVING
    - Stricture
    - Hernia
    - Adhesions
    - Volvulus
    - Intussusception/BID
    - Neoplasm
    - Gallstones
Clinical Features (unique to LBO)

- open loop (10-20%)  
  ▪ incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical presentation similar to SBO
- closed loop (80-90%) (dangerous)  
  ▪ competent ileocecal valve, resulting in proximal and distal occlusions  
  ▪ massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

Treatment

- surgical correction of obstruction (usually requires resection + temporary diverting colostomy)  
- volvulus requires sigmoidoscopic or endoscopic decompression followed by operative reduction if unsuccessful  
  ▪ if successful, consider sigmoid resection on same admission  
- cecal volvulus can be a true volvulus or a cecal ‘bascule’ (cecum folds anteriorly to the ascending colon producing a flap valve occlusion to cecal emptying) – both need surgical treatment

Prognosis

- overall mortality: 10%
- cecal perforation + feculent peritonitis: 20% mortality

Colonic Pseudo-Obstruction

Definition

- condition with symptoms of intestinal blockage without any physical signs of blockage  
- paralytic ileus of large bowel

Differential Diagnosis

- acute: toxic megacolon, trauma, post-operative (especially post orthopedic procedures with prolonged immobilization), neurologic disease, retroperitoneal disease, medications (narcotics, psychiatric)  
- chronic: neurologic disease (enteric, central, peripheral nervous system), scleroderma

Toxic Megacolon

Pathogenesis

- extension of inflammation into smooth muscle layer causing paralysis  
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

Etiology

- inflammatory bowel disease (ulcerative colitis > Crohn’s disease)  
- infectious colitis: bacterial (C. difficile, Salmonella, Shigella, Campylobacter), viral (cytomegalovirus), parasitic (E. histolytica)

Clinical Features

- infectious colitis usually present for >1 wk before colonic dilatation  
- diarrhea ± blood (but improvement of diarrhea may portend onset of megacolon)  
- abdominal distention, tenderness, ± local/general peritoneal signs (suggest perforation)  
- triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, anticholinergics), barium enema, colonoscopy

Diagnostic Criteria

- must have both colitis and systemic manifestations for diagnosis  
- radiologic evidence of dilated colon  
- three of: fever, HR >120, WBC >10.5, anemia  
- one of: fluid and electrolyte disturbances, hypotension, altered LOC

Investigations

- CBC (leukocytosis with left shift, anemia from bloody diarrhea), electrolytes, elevated CRP, ESR  
- metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings  
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra  
- CT: useful to assess underlying disease
Treatment
- NPO, NGT, stop constipating agents, correct fluid and electrolyte abnormalities, transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis, anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD, metronidazole for *C. difficile*)
- indications for surgery (50% improve on medical management)
  - worsening or persisting toxicity or dilation after 48-72 h
  - severe hemorrhage, perforation
  - high lactate and WBC especially for *C. difficile*
- procedure: subtotal colectomy + end ileostomy (may be temporary, with second operation for re-anastomosis later)

Prognosis
- average 25-30% mortality

Paralytic Ileus

Pathogenesis
- temporary paralysis of the myenteric plexus

Associations
- post-operative, intra-abdominal sepsis, medications (opiates, anesthetics, psychotropics),
  electrolyte disturbances (Na⁺, K⁺, Ca²⁺), *C. difficile*, inactivity

Treatment
- NGT decompression, NPO, fluid resuscitation, correct causative abnormalities (e.g. sepsis,
  medications, electrolytes), consider TPN for prolonged ileus
- post-operative: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d
- current interest in novel therapies such as gum chewing and pharmacologic therapy (opioid
  antagonists)

Ogilvie's Syndrome

- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- arises in bedridden patients with serious extraintestinal illness or trauma
- exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic
  deprivation to colon, unopposed parasympathetic tone, and interruption of sacral
  parasympathetic tone to distal bowel
- first presents with abdominal distention (>90%) ± tenderness
- later symptoms mimic true obstruction

Associations
- most common: trauma, infection, cardiac (MI, CHF)
- disability (long-term debilitation, chronic disease, bed-bound nursing home patients,
  paraplegia), drugs (narcotic use, laxative abuse, polypharmacy), other (recent orthopedic or
  neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal
  hematoma, diffuse carcinomatosis)

Investigations
- AXR: cecal dilatation – if diameter ≥12 cm, increased risk of perforation

Treatment
- treat underlying cause
- NPO, NGT
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical
  decompression (ostomy/resection) uncommon
- surgery (extremely rare): if perforation, ischemia, or failure of conservative management

Prognosis
- most resolve with conservative management

Use caution when giving antidiarrheals, especially with bloody diarrhea
**Intestinal Ischemia**

**Etiology**
- **acute**
  - arterio-occlusive mesenteric ischemia (AOMI)
  - thrombotic, embolic, extrinsic compression (e.g. strangulating hernia)
  - non-occlusive mesenteric ischemia (NOMI)
  - mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
  - mesenteric venous thrombosis (MVT)
  - consider hypercoagulable state (i.e. rule out malignancy), DVT (prevents venous outflow)
- **chronic**: usually due to atherosclerotic disease – look for CVD risk factors

**Clinical Features**
- **acute**: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, sepsis
- **chronic**: postprandial pain, fear of eating, weight loss
- **common sites**: SMA supplied territory, “watershed” areas of colon – splenic flexure, left colon, sigmoid colon

**Investigations**
- **laboratory**: leukocytosis (non-specific), lactic acidosis (late finding)
  - amylase, LDH, CK, ALP can be used to observe progress
  - hypercoagulability workup if suspect venous thrombosis
- **AXR**: portal venous gas, intestinal pneumatosis, free air if perforation
- **contrast CT**: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, pneumatosis
- **CT angiography** is the gold standard for acute arterial ischemia

**Treatment**
- fluid resuscitation, correct metabolic acidosis, NPO, NGT decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
- exploratory laparotomy
- angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, percutaneous transluminal angioplasty ± stent
- segmental resection of necrotic intestine
  - assess extent of viability; if extent of bowel viability is uncertain, a second look laparotomy 12-24 h later is mandatory

**Appendix**

**Appendicitis**

**Epidemiology**
- 6% of population, M>F
- 80% between 5-35 yr of age

**Pathogenesis**
- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure
  → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- **etiologies**
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecolith, obstructing neoplasm
  - other causes: parasites, foreign body

**Clinical Features**
- most reliable feature is progression of signs and symptoms
- low grade fever (38°C), rises if perforation
- abdominal pain then anorexia, N/V
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney’s point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
  - McBurney’s sign

**McBurney’s Sign**
Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side
• perioperative management
  • conserve bowel: resect as little as possible to avoid short gut syndrome
  • can alleviate symptoms, address complications, improve quality of life

Principles of Surgical Management
  • see Gastroenterology, G19

ADENOCARCINOMA
  • see GS21

Treatment
  • hydrate, correct electrolyte abnormalities
  • surgery (gold standard, 20% mortality with perforation especially in elderly) + antibiotic coverage
  • if localized abscess (palpable mass or large phlegmon on imaging and often pain >4-5 d), consider radiologic drainage + antibiotics x 14 d ± interval appendectomy in 6 wk (controversial)
  • appendectomy
    • laparoscopic vs. open (see sidebar)
    • complications: spillage of bowel contents, pelvic abscess, enterocutaneous fistula
    • perioperative antibiotics:
      • cefazolin + metronidazole (no post-operative antibiotic unless perforated)
      • other choices: 2nd/3rd generation cephalosporin for aerobic gut organisms
  • colonoscopy in the elderly to rule out other etiology (neoplasm)

Prognosis
  • mortality rate: 0.08% (non-perforated), 0.5% (perforated appendicitis)

Tumors of the Appendix

CARCINOID TUMORS (most common type)
  • see Tumors of Small Intestine: Carcinoid, GS21

ADENOCARCINOMA
  • 50% present as acute appendicitis
  • spreads rapidly to lymph nodes, ovaries, and peritoneal surfaces
  • treatment: right hemicolecction

Inflammatory Bowel Disease

• see Gastroenterology, G19

Principles of Surgical Management
  • can alleviate symptoms, address complications, improve quality of life
  • conserve bowel: resect as little as possible to avoid short gut syndrome
  • perioperative management
    • optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
    • hold immunosuppressive therapy pre-operative, provide pre-operative stress dose of corticosteroid if patient had recent steroid therapy, taper steroids post-operative
    • DVT prophylaxis: heparin (IBD patients at increased risk of thromboembolic events)
**Crohn’s Disease**

- see Gastroenterology, G20

**Treatment**
- surgery is NOT curative, but over lifetime ~70% of Crohn’s patients will have surgery
- indications for surgical management
  - failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), perianal disease
- surgical procedures
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, fistula
  - resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

**Complications of Treatment**
- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

**Prognosis**
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr

**Ulcerative Colitis**

- see Gastroenterology, G22

**Treatment**
- indications for surgical management
  - failure of medical management (including inability to taper steroids)
  - complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  - reduce cancer risk (1-2% risk per year after 10 yr of disease)
- surgical procedures
  - proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  - proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  - colectomy and IPAA ± rectal mucosectomy
- in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

**Complications of Treatment**
- early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomotic leak
- late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

**Prognosis**
- mortality: 5% over 10 yr
- total proctocolectomy will completely eliminate risk of cancer
- perforation of the colon is the leading cause of death from ulcerative colitis
Diverticular Disease

Definitions
- diverticulum: abnormal sac-like protrusion from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided

![Diagram of true and false diverticuli](image)

Figure 15. Diverticular disease – cross-sections of true and false diverticuli

Diverticulosis

Epidemiology
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

Pathogenesis
- risk factors
  - lifestyle: low-fiber diet (predispose to motility abnormalities and higher intraluminal pressure) inactivity, obesity
  - muscle wall weakness from aging and illness (e.g. Ehler-Danlos, Marfan’s)
- high intraluminal pressures cause outpouching to occur at point of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer, therefore increased risk of hemorrhage

Clinical Features
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive LGIB
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, abdominal pain

Treatment
- uncomplicated diverticulosis: high fiber, education
- diverticular bleed
  - initially workup and treat as any LGIB
  - if hemorrhage does not stop, resect involved region

Diverticulitis

Epidemiology
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

Pathogenesis
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula, or obstruction can ensue
- poor containment results in free perforation and peritonitis
Clinical Features
- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, N/V, urinary symptoms (with adjacent inflammation)
- complications (25% of cases)
  - abscess: palpable tender abdominal mass
  - fistula: colovesical (most common), colorectal, colovaginal, colocolonic
  - colonic obstruction: due to scarring from repeated inflammation
  - perforation: generalized peritonitis (feculent vs. purulent)
  - recurrent attacks rarely lead to peritonitis
- low-grade fever, mild leukocytosis common, occult or gross blood in stool rarely coexist with acute diverticulitis

Investigations
- AXR, upright CXR
  - localized diverticulitis (ileus, thickened wall, SBO, partial colonic obstruction)
  - free air may be seen in 30% with perforation and generalized peritonitis
- CT scan (test of choice): very useful for assessment of severity and prognosis; this is usually done with rectal contrast
  - 97% sensitive, 99% specific
  - increased soft tissue density within pericolic fat secondary to inflammation, diverticula secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), fistula
  - 10% of diverticulitis cannot be distinguished from carcinoma
- elective evaluations: establish extent of disease and rule out other diagnoses (polyps, malignancy) after resolution of acute episode
  - colonoscopy or barium enema and flexible sigmoidoscopy

Treatment
- uncomplicated: conservative management
- outpatient: clear fluids only until improvement and antibiotics (e.g. ciprofloxacin and metronidazole) 7-10 d to cover gram negative rods and anaerobes (e.g. B. fragilis)
- hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, fail to improve outpatient management
- treat with NPQ, IVF, IV antibiotics (e.g. IV ceftriaxone + metronidazole, ampicillin, gentamicin)
- indications for surgery
  - unstable patient with peritonitis
  - Hinchey stage 3-4
  - after 1 attack if immunosuppressed
  - consider after 2 or more attacks, recent trend is toward conservative management of recurrent mild/moderate attacks
- complications: generalized peritonitis, free air, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
- surgical procedures
  - for emergency or complex cases: Hartmann procedure: colon resection + colostomy and rectal stump + colostomy reversal in 3-6 mo
  - elective cases or minimal contamination of the abdominal cavity: consider colon resection + primary anastomosis

Prognosis
- mortality rates: 6% for purulent peritonitis, 35% for fecal peritonitis
- recurrence rates: 13-30% after first attack, 30-50% after second attack

Table 13. Hinchey Staging and Treatment for Diverticulitis

<table>
<thead>
<tr>
<th>Hinchey Stage</th>
<th>Description</th>
<th>Acute treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phlegmon/small pericolic abscess</td>
<td>Medical</td>
</tr>
<tr>
<td>2</td>
<td>Large abscess/fistula</td>
<td>Abscess drainage, resection ± primary anastomosis</td>
</tr>
<tr>
<td>3</td>
<td>Purulent peritonitis (ruptured abscess)</td>
<td>Hartmann procedure</td>
</tr>
<tr>
<td>4</td>
<td>Feculent peritonitis</td>
<td>Hartmann procedure</td>
</tr>
</tbody>
</table>

Figure 16. Hartmann procedure

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Area of diverticulitis and inflammation

Colostomy

Resection of diseased area and closure of distal rectal stump

Anastomosis in approximately 3 mo
Colorectal Neoplasms

Colorectal Polyp

Definition
- polyp: protuberance into the lumen of normally flat colonic mucosa
- sessile (flat) or pedunculated (on a stalk)

Epidemiology
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70

Clinical Features
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, mucus
- usually detected during routine endoscopy or familial/high risk screening

Pathology
- non-neoplastic
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <0.2 in, no clinical significance
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, carcinoids
- neoplastic
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
    - malignant risk due to associated adenomas (large bowel)
  - low malignant potential
    - most spontaneously regress or autoamputate
  - adenomas: premalignant, often carcinoma in situ
    - some may contain invasive carcinoma ("malignant polyp" – 3-9%): invasion into muscularis
    - malignant potential: villous > tubulovillous > tubular

Table 14. Characteristics of Tubular vs. Villous Polyps

<table>
<thead>
<tr>
<th></th>
<th>Tubular</th>
<th>Villous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Common (60-80%)</td>
<td>Less common (10%)</td>
</tr>
<tr>
<td>Size</td>
<td>Small (&lt;2 cm)</td>
<td>Large (usually &gt;2 cm)</td>
</tr>
<tr>
<td>Attachment</td>
<td>Pedunculated</td>
<td>Sessile</td>
</tr>
<tr>
<td>Malignant Potential</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Distribution</td>
<td>Even</td>
<td>Left-sided predominance</td>
</tr>
</tbody>
</table>

Investigations
- colonoscopy is the gold standard for diagnosis and treatment of colonic polyps
- CT colonography; increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscopy if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy

Treatment
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- surgical resection for those invading into muscularis (high risk of malignancy) and those too large to remove endoscopy
- follow-up endoscopy 1 yr later, then every 3-5 yr

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS

Pathogenesis
- autosomal dominant inheritance, mutation in adenomatous polyposis coli (APC) gene on chromosome 5q21

Clinical Features
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40s in attenuated FAP)
- extracolonic manifestations
  - carcinoma of small bowel (i.e. polyps in colon), bile duct, pancreas, stomach, thyroid, adrenal, small bowel
  - congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
  - virtually 100% lifetime risk of colon cancer (because of number of polyps)
Hereditary non-polyposis colorectal cancer – Lynch syndrome

Pathogenesis
- Autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1) resulting in microsatellite genomic instability and subsequent mutations
  - Microsatellite instability account for approximately 15% of all colorectal cancers

Clinical Features
- Early age of onset, right > left colon, synchronous and metachronous lesions
- Mean age of cancer presentation is 44 yr, lifetime risk 70-80% (M>F)
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome – high rates of extracolonic tumors (endometrial, ovarian, hepatobiliary, small bowel)

Diagnosis
- Amsterdam Criteria
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr old
  - FAP is excluded
- Genetic testing (80% sensitive) – colonoscopy mandatory even if negative
  - Refer for genetic screening individuals who fulfill EITHER the Amsterdam Criteria (as above) OR the revised Bethesda Criteria (see sidebar)
- Colonoscopy (starting age 20) annually
- Surveillance for extracolonic lesions

Treatment
- Total colectomy and ileorectal anastomosis with annual proctoscopy

• Variants
  ▪ Gardner’s syndrome: FAP + extraintestinal lesions (sebaceous cysts, osteomas, desmoid tumors)
  ▪ Turcot syndrome: FAP + CNS tumors (childhood cerebellar medulloblastoma)

Investigations
- Genetic testing (80-95% sensitive, 99-100% specific)
- If no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- If polyposis or APC gene mutation found: annual colonoscopy and consider surgery (see Figure 16); consider upper endoscopy to evaluate for periampullary tumors

Treatment
- Surgery indicated by age 17-20
- Total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- Doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER – LYNCH SYNDROME

Pathogenesis
- Autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1) resulting in microsatellite genomic instability and subsequent mutations

Clinical Features
- Early age of onset, right > left colon, synchronous and metachronous lesions
- Mean age of cancer presentation is 44 yr, lifetime risk 70-80% (M>F)
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- Colonoscopy (starting age 20) annually
- Surveillance for extracolonic lesions

Treatment
- Total colectomy and ileorectal anastomosis with annual proctoscopy

Colorectal Carcinoma

Epidemiology
- 4th most common cancer (after lung, prostate, and breast), 2nd most common cause of cancer death

Risk Factors
- Most patients have no specific risk factors
- Age >50 (dominant risk factor in sporadic cases), mean age is 70
- Genetic: FAP, HNPCC, family history of CRC
- Colonic conditions
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - Previous colorectal cancer (also gonadal or breast)
- Diet (increased fat, red meat, decreased fiber) and smoking
- DM and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

Pathogenesis
- Adenoma-carcinoma sequence; rarely arise de novo

5-yr Survival Rates for CRC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>II A</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>II B</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>II C</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>III A</td>
<td>73%</td>
<td>74%</td>
</tr>
<tr>
<td>III B</td>
<td>46%</td>
<td>45%</td>
</tr>
<tr>
<td>III C</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Revised Bethesda Criteria for HNPCC and Microsatellite Instability (MSI)
- Tumors from individuals should be tested for MSI in the following situations
  - Colorectal cancer diagnosed in a patient who is <50 yr
  - Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age
  - Colorectal cancer with the MSI-H histology diagnosed in a patient who is <60 yr
  - Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed <50 yr
  - Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

Elderly persons who present with iron-deficiency anemia should be investigated for colon cancer

Referral Criteria for Genetic Screening for APC
- To confirm the diagnosis of FAP (in patients with ≥100 colorectal adenomas)
- To provide pre-symptomatic testing for individuals at risk for FAP (1st degree relatives who are ≥10 yr old)
- To confirm the diagnosis of attenuated FAP (in patients with ≥20 colorectal adenomas)
Clinical Features
- often asymptomatic
- hematochezia/melena, abdominal pain, change in bowel habits
- others: weakness, anemia, weight loss, palpable mass, obstruction
- 20% patients have distant metastatic disease at time of presentation
- spread
  - direct extension, lymphatic, hematogenous (liver most common, lung, bone, brain; tumor of distal rectum → IVC → lungs)
  - peritoneal seeding: ovary, Blumer’s shelf (pelvic cul-de-sac)

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

- rectal cancer: pelvic MRI or endorectal ultrasound to determine T and N stage
- staging (see Table 16 and sidebar GS34): CT chest/abdomen/pelvis; bone scan, CT head only if laboratory: CBC, urinalysis, liver enzymes, liver function tests, carcinoembryonic antigen (CEA) (if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast enema)

<table>
<thead>
<tr>
<th>Table 15. Clinical Presentation of CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features</td>
</tr>
<tr>
<td>Spread: peritoneal seeding: ovary, Blumer’s shelf (pelvic cul-de-sac)</td>
</tr>
<tr>
<td>Symptoms: Weight loss, weakness, rarely obstruction</td>
</tr>
<tr>
<td>Signs: Fe-deficiency anemia, RLQ mass (10%)</td>
</tr>
</tbody>
</table>

Investigations
- colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema (“apple core” lesion) + sigmoidoscopy
- if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy
- laboratory: CBC, urinalysis, liver enzymes, liver function tests, carcinoembryonic antigen (CEA) (for pre-operative baseline, >5/10/L have worse prognosis)
- staging (see Table 16 and sidebar GS34): CT chest/abdomen/pelvis; bone scan, CT head only if lesions suspected
- rectal cancer: pelvic MRI or endorectal ultrasound to determine T and N stage

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary tumor found</td>
<td>N0 No regional node involvement</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
<td>N1 Metastasis in 1-3 regional nodes</td>
</tr>
<tr>
<td>T1</td>
<td>Invasion into submucosa</td>
<td>N2 Metastasis in 4 or more regional nodes</td>
</tr>
<tr>
<td>T2</td>
<td>Invasion into muscularis propria</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Invasion through muscularis propria and into serosa</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Invasion into adjacent structures or organs</td>
<td></td>
</tr>
</tbody>
</table>

Treatment
- colon cancer
  - wide surgical resection of lesion and regional lymphatic drainage; usually colectomy with primary anastomosis
  - curative: wide resection of lesion (2 in margins) with nodes and mesentery
  - palliative: if distant spread, local control for hemorrhage or obstruction
  - care is taken to not spread tumor by unnecessary palpation
  - cancer-bearing portion of colon is removed according to vascular distribution of segment
  - adjuvant chemotherapy (5-FU or oral capecitabine with oxaliplatin) can be considered for stages II or III
- rectal cancer
  - choice of operation depends on individual case; types of operations (see Figure 18)
  - low anterior resection of rectum (LAR): curative procedure of choice if adequate distal margins; uses technique of total mesorectal excision
  - abdominoperineal resection of rectum (APR): if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus – permanent end colostomy required
  - local excision: for select T1 lesions only
  - palliative procedures: electrocoagulation or laser photocoagulation for unresectable cancers for symptomatic relief
  - adjuvant therapy
    - combined neoadjuvant chemoradiation therapy followed by post-operative adjuvant chemotherapy for stages II and III

Follow-Up
- currently there are no data suggesting optimal follow-up
- combination of periodic CT chest/abdomen/pelvis, CEA, and colonoscopy is recommended
- CEA to monitor for initial response to treatment, and to assess for recurrence q3mo (not a screening test)
- intensive follow-up improves overall survival in low-risk patients

Table 17. Clinical Presentation of CRC

- spread
- 20% patients have distant metastatic disease at time of presentation
- others: weakness, anemia, weight loss, palpable mass, obstruction
- often asymptomatic

Follow-Up
- 10 yr incidence of local relapse was significantly lower in the pre-operative CRT group than in the post-operative group (7.1% vs. 10.1%, p=0.049)
- Overall survival at 10 yr was similar at ~60% for patients treated with pre-operative or post-operative CRT (p=0.35)
- Disease-free survival rates at 10 yr were similar at ~60% for patients treated with pre-operative or post-operative CRT (p=0.54)
- No significant difference was detected for 10 yr incidence of distant metastases (pre-operative CRT 23.9% vs. post-operative CRT 29.8%, p=0.19)

Conclusion: There is long-term reduction in local recurrence of stage II to III rectal cancer with pre-operative chemotherapy, but no improvement in overall survival or distant recurrence of disease.
**Angiodysplasia**

**Definition**
- vascular anomaly: focal submucosal venous dilatation and tortuosity

**Clinical Features**
- most frequently in right colon of patients >60 yr old
- bleeding typically intermittent, rarely massive, not usually hypotensive (melena, anemia, guaiac positive stools)

**Investigations**
- colonoscopy: cherry red spots, branching pattern from central vessel
- angiography: early-filling vein, vascular tuft, delayed emptying vein; rarely active bleeding
- RBC technetium-99 scan
- barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

**Treatment**
- none if asymptomatic
- cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

**Volvulus**

**Definition**
- rotation of segment of bowel about its mesenteric axis
- sigmoid (65%), cecum (30%), transverse colon (3%), splenic flexure (2%)
- 5-10% of large bowel obstruction; 25% of intestinal obstruction during pregnancy

**Risk Factors**
- age (50% of patients >70 yr: stretching/elongation of bowel with age is a predisposing factor)
- high fiber diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, institutionalization (less frequent evacuation of bowels)
- congenital hypermobile cecum

**Clinical Features**
- symptoms due to bowel obstruction (see Bowel Obstruction, GS24) or intestinal ischemia (see Intestinal Ischemia, GS28)
- colicky abdominal pain, persistence of pain between spasms, abdominal distention, vomiting

**Investigations**
- AXR (classic findings): "omega", "bent inner-tube", "coffee-bean" signs
- barium/Gastrografin" enema: "ace of spades" (or "bird’s beak") appearance due to funnel-like luminal tapering of lower segment towards volvulus
- sigmoidoscopy or colonoscopy as appropriate
- CT

**Treatment**
- initial supportive management (same as initial management for bowel obstruction (see Bowel Obstruction, GS24)
- cecum
  - nonsurgical
    - may attempt colonoscopic detorsion and decompression
  - surgical
    - right colectomy + ileotransverse colonic anastomosis
- sigmoid
  - nonsurgical
    - decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
  - subsequent elective surgery recommended (50-70% recurrence)
  - surgical: Hartmann procedure (if urgent)
    - indications: strangulation, perforation, or unsuccessful endoscopic decompression
Fistula

Definition
• abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, entero-enteric)

Etiology
• foreign object erosion (e.g. gallstone, graft)
• inflammatory states (e.g. infection, IBD [especially Crohn’s], diverticular disease)
• iatrogenic/surgery (e.g. post-operative anastomotic leak, radiation)
• congenital, trauma
• neoplastic

Investigations
• U/S, CT scan, fistulogram
• measure amount of drainage from fistula

Treatment
• decrease secretion: octreotide/somatostatin/omeprazole
• surgical intervention: dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis

Stomas

Definition
• an opening of the GI tract onto the surface of the abdomen wall

Ileostomy
• usually positioned in RLQ; ileum is brought through rectus abdominus muscles
• indications: after protocolectomy for ulcerative colitis, in some cases of Crohn's disease or familial polyposis
• conventional ileostomy: discharges small quantities of liquid material continuously; appliance (plastic bag attached to a sheet of protective material) required at all times
• continent ileostomy: reservoir is constructed from distal ileum, emptied by inserting catheter into stoma several times a day; rarely used, has mostly been replaced by ileal pouch anal anastomosis

Colostomy
• indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
• colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
• most common permanent colostomy is a sigmoid colostomy – expels stool once per day, no appliance required
• chronic paracolostomy hernia is a common complication

Complications (10%)
• obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
• peri-ileostomy abscess and fistula
• skin irritation
• prolapse or retraction
• diarrhea (excessive output)
Anorectum

Hemorrhoids

Etiology
- vascular and connective tissue complexes form a plexus of dilated veins (cushion)
  - internal: superior hemorrhoidal veins, above dentate line, portal circulation
  - external: inferior hemorrhoidal veins, below dentate line, systemic circulation

Risk Factors
- increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal HTN, heavy lifting

Clinical Features and Treatment
- internal hemorrhoids
  - engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  - 1st degree: bleed but do not prolapse through the anus
    - treatment: high fiber/bulk diet, sitz baths, steroid cream, paroxime (Anusol®), rubber band ligation, sclerotherapy, photoacoagulation
  - 2nd degree: bleed, prolapse with straining, spontaneous reduction
    - treatment: rubber band ligation, photoacoagulation
  - 3rd degree: bleed, prolapse, requires manual reduction
    - treatment: same as 2nd degree, but may require closed hemorrhoidectomy
  - 4th degree: bleed, permanently prolapsed, cannot be manually reduced
    - treatment: closed hemorrhoidectomy
- external hemorrhoids
  - dilated venules usually mildly symptomatic
  - PAIN after bowel movement, associated with poor hygiene
  - medical treatment: dietary fiber, stool softeners, steroid cream (short course), paroxime (Anusol®), avoid prolonged straining
  - thrombosed hemorrhoids are very painful
  - resolve within 2 wk, may leave excess skin = perianal skin tag
  - treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment

Table 17. Signs and Symptoms of Internal vs. External Hemorrhoids

<table>
<thead>
<tr>
<th>Internal Hemorrhoids</th>
<th>External Hemorrhoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless BRBPR</td>
<td>Sudden severe perianal pain</td>
</tr>
<tr>
<td>Rectal fullness or discomfort</td>
<td>Perianal mass</td>
</tr>
<tr>
<td>Mucus discharge</td>
<td></td>
</tr>
</tbody>
</table>

Anal Fissures

Definition
- tear of anal canal below dentate line (very sensitive squamous epithelium)
- 90% posterior midline, 10% anterior midline
- if off midline: consider other possible causes such as IBD, STDs, TB, leukemia, or anal carcinoma
- repetitive injury cycle after first tear:
  - sphincter spasm occurs preventing edges from healing and leads to further tearing
  - ischemia may ensue and contribute to chronicity

Etiology
- forceful dilation of anal canal: large, hard stools and irritant diarrheal stools
- tightening of anal canal secondary to nervousness/pain leads to further tearing
- others: habitual use of cathartics, childbirth

Clinical Features
- acute fissure
  - very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  - treatment is conservative: stool softeners, bulking agent, sitz baths (heals 90%)
- chronic fissure (anal ulcer)
  - triad: fissure, sentinel skin tags, hypertrophied papillae

Always rule out more serious causes (e.g. colon CA) in a person with hemorrhoids and rectal bleeding
- treatment
  - stool softeners, bulking agents, sitz baths
  - topical nitroglycerin or nifedipine: increases local blood flow, promoting healing and relieves sphincter spasm
  - lateral internal anal sphincterotomy (most effective): objective is to relieve sphincter spasm → increases blood flow and promotes healing; but 5% chance of fecal incontinence therefore not commonly done
- alternative treatment
  - botulinum toxin: inhibits release of acetylcholine (ACh), reducing sphincter spasm

### Anorectal Abscess

#### Definition
- infection in one or more of the anal spaces
- usually bacterial infection of blocked anal gland at the dentate line
  - *E. coli, Proteus, Streptococci, Staphylococci, Bacteroides, anaerobes*

![Figure 22. Different types of perianal abscesses](image)

**Clinical Features**
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator), or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

**Treatment**
- I&D
  - curative in 50% of cases
  - 50% develop anorectal fistulas
  - may require antibiotics if diabetic, heart murmur, or cellulitis

### Fistula-In-Ano

#### Definition
- anal fistula from rectum to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

#### Etiology
- see *Fistula, GS37*
- same perirectal process as an anal abscess, therefore usually associated with an abscess
- other causes: post-operative, trauma, anal fissure, malignancy, radiation proctitis

**Clinical Features**
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract
Treatment
- identification
  - internal opening
    - Goodsall’s rule
      - fistulas originating anterior to a transverse line through the anus will have a straight course and exit anteriorly, whereas those originating posterior to the transverse line will begin in the midline and have a curved tract
  - fistulous tract
    - probing or fistulography under anesthesia
- surgery
  - fistulotomy: unroof tract from external to internal opening, allow drainage, heals by secondary intention
  - low lying fistula (does not involve external sphincter) → primary fistulotomy
  - high lying fistula (involves external sphincter) → staged fistulotomy with Seton suture placed through tract
    - promotes drainage
    - promotes fibrosis and decreases incidence of incontinence
    - delineates anatomy
    - usually done to spare muscle cutting

Post-Operative
- sitz baths, irrigation, and packing to ensure healing proceeds from inside to outside

Complications
- recurrence
- rarely fecal incontinence

Pilonidal Disease
Definition
- chronic recurring abscess or chronic draining sinus in sacrococcygeal area

Epidemiology
- occurs most frequently in young men age 15-40 yr; rare in >50 yr

Etiology
- obstruction of the hair follicles in this area → formation of cysts, sinuses, or abscesses

Clinical Features
- asymptomatic until acutely infected, then pain/tenderness, purulent discharge, inspissated hair

Treatment
- acute abscess
  - I&D (often performed by primary care doctors)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery
  - indication: failure of healing after I&D, recurrent disease, complex disease
  - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention, primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

Rectal Prolapse
Definition
- protrusion of some or all of rectal mucosa through external anal sphincter

Epidemiology
- extremes of ages: <5 yr old and >5th decade
- 85% women

Etiology
- lengthened attachment of rectum secondary to constant straining
- 2 types
  I. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  II. true/complete (most common): full thickness extrusion of rectal wall, concentric folds in:
    - first degree: prolapse includes mucocutaneous junction
    - second degree: without involvement of mucocutaneous junction
    - third degree (internal intussusception): prolapse is internal, concealed, or occult
Risk Factors
- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility

Clinical Features
- extrusion of mass with increased intra-abdominal pressure:
  - straining, coughing, laughing, Valsalva
- difficulty in bowel regulation:
  - tenesmus, constipation, fecal incontinence
- permanently extruded rectum with excoriation, ulceration, and constant soiling
- may be associated with urinary incontinence or uterine prolapse

Treatment
- Type I
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- Type II
  - conservative: reduce if possible
  - surgery: abdominal, perineal, transsacral approaches

Anal Neoplasms

ANAL CANAL
Squamous Cell Carcinoma of Anal Canal (Above Dentate Line)
- most common tumor of anal canal (75%)
- anus prone to human papillomavirus (HPV) infection, therefore at risk for anal squamous intraepithelial lesions (ASIL)
  - high grade squamous intraepithelial lesion (HSIL) and low grade squamous intraepithelial lesion (LSIL) terminology used
- clinical features: anal bleeding, pain, mass, ulceration, pruritus; 25% asymptomatic
- treatment: chemotherapy ± radiation ± surgery
- prognosis: 80% 5 yr survival

Malignant Melanoma of Anal Canal
- 3rd most common site for primary malignant melanoma after skin, eyes
- aggressive, distant metastases common at time of diagnosis
- treatment: wide excision or APR ± chemoradiation
- prognosis: <5% 5 yr survival

ANAL MARGIN
- clinical features and treatment as for skin tumors elsewhere
- squamous and basal cell carcinoma, Bowen’s disease (SCC in situ), and Paget’s disease

Liver

Figure 26. Anatomy of liver
Liver Cysts

Table 18. Characteristics of Liver Cysts

<table>
<thead>
<tr>
<th>Description</th>
<th>Simple Cysts</th>
<th>Polycystic Liver Disease</th>
<th>Choledochal Cysts</th>
<th>Hydatid (Cystic Echinococcosis)</th>
<th>Cystadenoma (Premalignant)/Cystadenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contain clear fluid that do not communicate with the intrahepatic biliary tree</td>
<td>Several cysts that replace much of the liver</td>
<td>Congenital malformations of pancreato胆管 tree high risk of malignancy majority present before age 10</td>
<td>Infection with parasite Echinococcus granulosus associated with exposure to dogs, sheep, and cattle in Southern Europe, Middle East, Australasia, South America</td>
<td>Rare cystic tumors that occur in the liver parenchyma or the extrahepatic bile ducts Cystadenocarcinoma is an invasive carcinoma</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Usually asymptomatic or may have multiple simple cysts</td>
<td>Progressive 50% associated with polycystic kidney disease</td>
<td>Recurrent abdominal pain intermittent jaundice RUQ mass Cholangitis, pancreatitis</td>
<td>Asymptomatic mass chronic pain hepatomegaly</td>
<td>Upper abdominal mass Abdominal pain Anorexia</td>
</tr>
<tr>
<td>Investigations</td>
<td>U/S: Used for diagnosis and follow-up CT: well demarcated lesion that does not enhance with contrast</td>
<td>U/S</td>
<td>U/S</td>
<td>Anti-Echinococcus Ab (IgG) U/S CT: calcified mass Needle biopsy</td>
<td>Appear as complex cysts: internal septae, papillary projections, irregular lining Need histology for definite diagnosis</td>
</tr>
<tr>
<td>Treatment</td>
<td>Not required unless very large Monitor if &gt;4 cm</td>
<td>Only if symptomatic partial liver resection drainage</td>
<td>Complete excision of cysts liver transplant if cyst involves intrahepatic bile ducts Carol’s disease</td>
<td>Albendazole (anti-helminthic) – cure up to 30% Surgical (risk of spillage into abdomen): Conservative: open endocystectomy or PAIR (Percutaneous Aspiration, Injection of protoscolicidal agent, Re-aspiration) Radical: partial hepatectomy or total pericystectomy</td>
<td>All complex, multiloculated cysts (except echinococcal) should be excised because of malignancy risk</td>
</tr>
<tr>
<td>Complications</td>
<td>Intracystic hemorrhage</td>
<td>Biliary cirrhosis, portal HTN, rupture, cholangiocarcinoma Abnormal pancreato胆管 junction is associated with increased risk of malignancy</td>
<td>Inferior vena cava compression rupture can cause biliary colic, jaundice, cholangitis, pancreatitis, or anaphylactic reaction</td>
<td>Cystadenocarcinoma can invade adjacent tissues and metastasize</td>
<td></td>
</tr>
</tbody>
</table>

Liver Abscesses

Etiology
- types
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *E. coli, Klebsiella, Proteus, Strep. milleri*
  - parasitic (amoebic): *Entamoeba histolytica, Echinococcal cyst*
  - fungal: *Candida*
- sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features
- fever, malaise, chills, anorexia, weight loss, abdominal pain, nausea
- RUQ tenderness, hepatomegaly, jaundice

Investigations
- leukocytosis, anemia, elevated liver enzymes, hemagglutination titres for *Entamoeba* antibodies
- U/S, CXR (right basilar atelectasis/effusion), CT, cyst aspiration with C&S

Treatment
- treat underlying cause
- generally will treat initially with antibiotics alone and add surgical or percutaneous drainage and IV antibiotics for larger abscesses (initially ceftriaxone + metronidazole or pipercillin/tazobactam)
Prognosis
- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition

Neoplasms

Benign Liver Neoplasms

Hemangioma (cavernous)
- pathogenesis: most common benign hepatic tumor; results from malformation of angioblastic fetal tissue
- risk factors: F:M = 3:1
- clinical features
  - usually small and asymptomatic
  - consumptive coagulopathy if giant (in children)
- investigations
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement and delayed venous emptying), U/S (homogenous hyperechoic mass), arteriography (rarely used; “cotton wool” appearance), MRI
  - biopsy may result in hemorrhage
- treatment
  - usually none unless tumor bleeds or is symptomatic, then excision by lobectomy or enucleation

Focal Nodular Hyperplasia
- pathogenesis: unclear, may be regenerative response to hyperperfusion from anomalous arteries at center of nodule
- risk factors: female, age 20-50
- clinical features: asymptomatic, rarely grows or bleeds, no malignant potential
- investigations: central stellate scar on CT scan; MRI, biopsy may be required
- treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential) → often resected

Adenoma
- definition: benign glandular epithelial tumor
- risk factors: female, age 20-50, estrogen (OCP, pregnancy)
- clinical features: asymptomatic, 25% present with RUQ pain or mass, may present with bleeding
- investigations: CT (well-demarcated masses, often heterogeneous enhancement on arterial phase, isodense on venous phase without washout of contrast), U/S, MRI, biopsy often needed
- treatment
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to hepatocellular carcinoma and spontaneous rupture/hemorrhage

Malignant Liver Neoplasms

Primary
- usually hepatocellular carcinoma (HCC)/hepatoma
- others include angiosarcoma, hepatoblastoma, hemangiendothelioma
- epidemiology: 3rd leading cause of cancer death worldwide, 9th in United States; highest in Africa, China, Taiwan
- risk factors
  - chronic liver inflammation: chronic hepatitis B (inherently oncogenic) and C, cirrhosis (especially macronodular), hemochromatosis, α1-antitrypsin deficiency
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, Betel nuts
  - chemical carcinogens ( aflatoxin, microcystin, vinyl chloride – associated with angiosarcoma)
- clinical features
  - RUQ discomfort, right shoulder pain
  - jaundice, weakness, weight loss, ± fever (if central tumor necrosis)
  - hepatomegaly, bruit, hepatic friction rub
  - ascites with blood (sudden intra-abdominal hemorrhage)
  - paraneoplastic syndromes – hypoglycemia, hypercalcemia, erythrocytosis, watery diarrhea
  - metastasis: lung, bone, brain, peritoneal seeding

Secondary liver metastases are common in many cancers, with some studies showing a prevalence of 40-50% amongst patients with extrahepatic cancers. They commonly arise from breast, lung, and colorectal cancers. For metastases secondary to colorectal cancer, surgical resection offers the greatest likelihood of cure.
Liver Transplantation

Table 19. Conditions Leading to Transplantation

<table>
<thead>
<tr>
<th>Parenchymal Disease</th>
<th>Cholestatic Disease</th>
<th>Inborn Errors</th>
<th>Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B or C</td>
<td>Biliary atresia**</td>
<td>α1-antitrypsin deficiency</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>Primary biliary cirrhosis</td>
<td>Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>Sclerosing cholangitis</td>
<td>Hemochromatosis</td>
<td></td>
</tr>
<tr>
<td>Congenital hepatic fibrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Autoimmune hepatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptogenic cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug induced hepatotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Leading cause in adults; **Leading cause in children

Clinical Indications
- Year referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially:
  - Decompensated cirrhosis (ascites, esophageal variceal hemorrhage, spontaneous hepatic encephalopathy, coagulopathy, progressive jaundice, severe fatigue)
  - Unresectable primary liver cancers
  - Fulminant hepatic failure
  - End-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate

Criteria for Transplantation
- Model for End-Stage Liver Disease (MELD): prognostic model to estimate 3 mo survival and disease severity if patient does not receive transplant; based on creatinine, bilirubin, INR; MELD scores from 6-40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: classification system to assess the prognosis and mortality of liver disease; patient must have ≥7 points (Class B)

Contraindications
- Active alcohol/substance abuse
- Extrahepatic malignancy within 5 yr
- Advanced cardiopulmonary disease
- Active uncontrolled infection
Post-Operative Complications
- primary non-function (graft failure): urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: HTN, renal disease, DM, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

Prognosis
- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%

Biliary Tract

Cholelithiasis

Definition
- the formation of gallstones

Pathogenesis
- imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
- excessive hepatic cholesterol secretion → bile salts and lecithin are “overloaded” → supersaturated cholesterol can precipitate and form gallstones
- North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors
- cholesterol stones
  - obesity, age <50
  - estrogens: female, multiparity, OCPs
  - ethnicity: First Nations heritage (especially Pima Indians) > Caucasian > Black
  - terminal ileal resection or disease (e.g. Crohn’s disease)
  - impaired gallbladder emptying: starvation, TPN, DM
  - rapid weight loss: rapid cholesterol mobilization and biliary stasis
  - pigment stones (contain calcium bilirubinate)
  - cirrhosis
  - chronic hemolysis
  - biliary stasis (strictures, dilation, biliary infection)
  - protective factors: statins, vitamin C, coffee, exercise

Outcomes of Living and Deceased Donor Liver Transplant Recipients With Hepatocellular Carcinoma: Results of the A2ALL Cohort


Purpose: To compare the overall survival and hepatocellular carcinoma (HCC) recurrence rates after living donor liver transplantation (LDLT) vs. deceased donor liver transplantation (DDLT) in a series of patients with HCC.

Methods: Study conducted between 1998 and 2009 at nine clinical centers. 229 patients with HCC undergoing liver transplantation included, with approximately 57% transplanted prior to MELD score implementation.

Results: The 5 yr survival rates were 59% in LDLT recipients and 66% in DDLT recipients (HR=1.32; p=0.27). Recurrence-free survival between LDLT and DDLT recipients did not differ (without using MELD score HR=1.13; p=0.3). Using MELD score (HR=1.32, p=0.01), recurrence rates at 5 yr were lower in LDLT recipients (HR=2.33; p=0.04), but not significantly different than in DDLT recipients following introduction of MELD scoring (HR=1.36, p=0.57).

Conclusion: Overall survival was not significantly different between LDLT and DDLT recipients. Although the HCC recurrence rate was higher in LDLT recipients, it was most likely due to more advanced HCC prior to transplant and less liver-directed HCC therapy compared to DDLT.

Summary of Biliary Tract Conditions

<table>
<thead>
<tr>
<th>Gallbladder</th>
<th>Asymptomatic Pain</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis</td>
<td>(majority)</td>
<td>+ Pain</td>
</tr>
<tr>
<td>Biliary Colic</td>
<td>(majority)</td>
<td>+ Pain</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td></td>
<td>+ Pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Common</th>
<th>Asymptomatic Pain</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Bile Duct</td>
<td>(majority)</td>
<td>+ Pain</td>
</tr>
<tr>
<td>Cholecystoenteric fistula may lead to gallstone ileus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors for Cholesterol Stones
- 4F's
  - Fasting
  - Female
  - Fertile
  -Forties

Figure 27. Gallstone disease

Clinical Presentation
- asymptomatic (80%)
  - most do NOT require treatment
  - consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli’s disease, porcelain or calcified gallbladder), sickle cell disease, pediatric patient, bariatric surgery, immunosuppression
Clinical Features
- steady, severe dull pain in epigastrium or RUQ for minutes to hours, crescendo-decrescendo pattern
- may present with chest pain
- N/V
- frequently occurs at night or after fatty meal, not after fasting
- can radiate to right shoulder or scapula
- patients often restless
- no peritoneal findings, no systemic signs

Investigations
- normal blood work: CBC, electrolytes, LFTs, bilirubin, amylase
- U/S shows cholelithiasis, may show stone in cystic duct

Treatment
- analgesia, hydration during colic episode
- elective cholecystectomy (95% success)
- laparoscopic cholecystectomy, hospital stay, and morbidity during the waiting period for elective cholecystectomy for patients with uncomplicated biliary colic due to gallstones. Results: One trial with 75 participants, average age 43 yr. Early laparoscopic cholecystectomy (<24 h vs. delayed mean wait period 4.2 mo). The proportion of serious adverse events was lower in the early vs. delayed group (0% vs. 22.5%, respectively). There was a shorter hospital stay in the early group (MD -1.25 d, 95% CI -2.05 to -0.45) and a shorter operating time in the early group (MD -1.95 min, 95% CI -3.00 to -0.90). There was no difference in the proportion of patients requiring conversion to open cholecystectomy in the two groups. Conclusion: Early laparoscopic cholecystectomy (<24 h of diagnosis of biliary colic) decreased morbidity during the waiting period for elective laparoscopic cholecystectomy, hospital stay, and operating time.

Pathogenesis
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see Acute Cholecystitis, GS47)

Clinical Features
- often have history of biliary colic
- severe constant (hours to days) epigastric or RUQ pain, anorexia, N/V, low grade fever (<38.5°C)

Acute Cholecystitis
Pathogenesis
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see Acute Cholecystitis, GS47)
• focal peritoneal findings: Murphy’s sign, palpable, tender gallbladder (in 33%)
• Boas’ sign: right subscapular pain

**Investigation**
- blood work: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT, and ALP
- U/S: 98% sensitive, consider HIDA scan if U/S negative

**Complications**
- gallbladder mucocele (hydrops): long-term cystic duct obstruction results in mucous accumulation in gallbladder (clear fluid)
- gangrene (20%), perforation (2%): result in abscess formation or peritonitis
- empyema of gallbladder: supplicative cholecystitis, pus in gallbladder + sick patient
- cholecystoenteric fistula, from repeated attacks of cholecystitis, can lead to gallstone ileus
- emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall, or pericholecystic space (risk in diabetic patient)
- organisms involved in secondary infection: *E. coli*, *Klebsiella*, *Enterococcus*
- Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct

**Treatment**
- admit, hydrate, NPO, NGT (if persistent vomiting from associated ileus), analgesics once diagnosis is made
- antibiotics
  - cefazolin if uncomplicated cholecystitis
- cholecystectomy
  - early (within 72 h) vs. delayed (after 6 wk)
    - equal morbidity and mortality
    - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
    - emergent OR indicated if high risk, e.g. emphysematous
  - laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-operative pain, increased risk of bile duct injury
- intraoperative cholangiography (IOC)
  - indications: clarify bile duct anatomy, obstructive jaundice, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), single faceted stone in gallbladder, bilirubin >8 mg/dL.
  - percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated

### Acalculous Cholecystitis

**Definition**
- acute or chronic cholecystitis in the absence of stones

**Pathogenesis**
- typically due to gallbladder ischemia, stasis

**Risk Factors**
- DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis

**Clinical Features**
- see **Acute Cholecystitis**, GS46
- occurs in 20% of cases of acute cholecystitis

**Investigations**
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see **Acute Cholecystitis**, GS46)
- CT or HIDA scan

**Treatment**
- broad-spectrum antibiotics, cholecystectomy
- if patient unstable → cholecystostomy

### Choledocholithiasis

**Definition**
- stones in CBD

**Clinical Features**
- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, fluctuating jaundice
• primary vs. secondary stones
  ▪ primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, CF)
  ▪ secondary: formed in gallbladder (85% of cases in U.S.)

Investigations
• CBC: usually normal; leukocytosis suggests cholangitis
• LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GGT later
• amylase/lipase: to rule out gallstone pancreatitis
• U/S: intra-/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
• ERCP, PTC
• MRCP (90% sensitive, almost 100% specific, not therapeutic)

Complications
• cholangitis, pancreatitis, biliary stricture, and biliary cirrhosis

Treatment
• if no evidence of cholangitis: treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients

Acute Cholangitis

Pathogenesis
• obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration and biliary sepsis – may be life-threatening, especially in elderly

Etiology
• choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), biliary stent
• organisms: *E. coli*, *Klebsiella*, *Pseudomonas*, *Enterococcus*, *B. fragilis*, *Proteus*

Clinical Features
• Charcot's triad: fever, RUQ pain, jaundice
• Reynold's pentad: fever, RUQ pain, jaundice, shock, confusion
• may have N/V, abdominal distention, ileus, acholic stools, tea-colored urine (elevated direct bilirubin)

Investigations
• CBC: elevated WBC + left shift
• may have positive blood cultures
• LFTs: obstructive picture (elevated ALP, GGT, and conjugated bilirubin, mild increase in AST, ALT)
• amylase/lipase: rule out pancreatitis
• U/S: intra-/extra-hepatic duct dilatation

Treatment
• initial: NPO, fluid and electrolyte resuscitation, ± NGT, IV antibiotics (treats 80%)
• biliary decompression
  ▪ ERCP + sphincterotomy: diagnostic and therapeutic
  ▪ PTC with catheter drainage: if ERCP not available or unsuccessful
  ▪ laparotomy with CBD exploration and T-tube placement if above fails
• all patients should also have a cholecystectomy, unless contraindicated

Prognosis
• suppurative cholangitis mortality rate: 50%

Gallstone Ileus

Pathogenesis
• repeated inflammation causing a cholecystoenteric fistula (usually duodenal) → large gallstone enters the gut and impacts at or near the ileocecal valve, causing a true bowel obstruction (note: ileus is a misnomer in this context)

Clinical Features
• crampy abdominal pain, N/V (see *Bowel Obstruction*, GS24)

Investigations
• AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, air in biliary tree (pneumobilia) (40%)
• CF: biliary tract air, obstruction, gallstone in intestine
• Rigler's triad: pneumobilia (air in biliary tree), small bowel obstruction (partial or complete), gallstone (usually in right iliac fossa)

Laparoscopic vs. Open Cholecystectomy
• Shorter operating time
• Shorter length of stay
• Shorter sick leave
• Shorter time to return to daily activities
• Less post-operative pain
• Decreased use of post-operative analgesia
• Decreased reduction in pulmonary function*
• Fewer pulmonary complications
• Decreased acute phase response
• Less impairment in intestinal motility*

Open Cholecystectomy
• Lower conversion rates to open surgery (for mini-laparotomies)

American Society of Gastrointestinal Endoscopy 2010 Predictors for Risk of CBD Stones
• Very strong:
  ▪ CBD stone on ultrasound
  ▪ Clinical ascending cholangitis
  ▪ Bilirubin >4 mg/dL
• Strong:
  ▪ CBD dilated >6 mm on ultrasound
  ▪ Bilirubin 1.8-4 mg/dL
• Moderate:
  ▪ Abnormal liver test (besides bilirubin)
  ▪ Age >55 yr
  ▪ Clinical gallstone pancreatitis

Charcot's Triad
Fever, RUQ pain, jaundice

Reynold's Pentad
Fever, RUQ pain, jaundice, shock, confusion

Rigler's Triad of Gallstone Ileus
• Pneumobilia
• Small bowel obstruction
• Gallstone

Pneumobilia
• *Enterobacter*
• *Proteus*, *Pseudomonas*
• *Serratia*

Common Bacteria in Biliary Tract
KEEPS
*Klebsiella*
*Enterococcus*
*E. coli*, *Enterobacter*
*Proteus*, *Pseudomonas*
*Serratia*
### Treatment
- Fluid resuscitation, NGT decompression
- Surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
- May close fistula surgically or manage expectantly (can resolve spontaneously)
- Cholecystectomy either during enterolithotomy or after recovery if patient experiences gallbladder symptoms

### Carcinoma of the Gallbladder

#### Risk Factors
- Chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (*Salmonella, Helicobacter*), abnormal pancreaticobiliary duct junction

#### Clinical Features
- Majority are adenocarcinoma
- May be incidental finding on elective cholecystectomy (~1% of elective cholecystectomies)
- Many patients are asymptomatic until late
- Local: non-specific RUQ pain, palpable RUQ mass
- Courvoisier’s gallbladder: an enlarged, often palpable gallbladder in a patient with carcinoma of the head of the pancreas; associated with jaundice due to obstruction of the CBD
- Systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- Early local extension to liver, may extend to stomach, duodenum
- Early metastasis common to liver, lung, bone

#### Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, fixed mass
- Endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, good for staging, allows sampling of bile for cytology
- Abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

#### Treatment
- If carcinoma of the gallbladder is suspected pre-operatively, an open cholecystectomy should be considered to avoid tumor seeding of the peritoneal cavity
- Confined to mucosa (rare): cholecystectomy
- Beyond mucosa: cholecystectomy, en bloc wedge resection of 3–5 cm underlying liver, dissection of hepatoduodenal lymph nodes

#### Prognosis
- Poor 5 yr survival (10%) as gallbladder carcinoma is often detected late
- Better outcomes when detected incidentally following cholecystectomy

### Cholangiocarcinoma

#### Definition
- Malignancy of extra- or intrahepatic bile ducts

#### Risk Factors
- Age 50–70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, *Clonorchis sinensis* infection (liver fluke), chronic intrahepatic stones (hepatolithiasis)

#### Clinical Features
- Majority are adenocarcinomas
- Gradual signs of biliary obstruction: jaundice, pruritus, dark urine, pale stools
- Anorexia, weight loss, RUQ pain, Courvoisier’s sign (if CBD obstructed), hepatomegaly
- Early metastases are uncommon, but commonly tumor grows into portal vein or hepatic artery
- Klatskin tumor: cholangiocarcinoma located at bifurcation of common hepatic duct

#### Investigations
- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup
Treatment
- if resectable: biliary drainage and wide excision margin
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)
- chemotherapy ± radiotherapy
- role for transplantation in some patients with Klatskins tumors

Prognosis
- radiotherapy useful for additional palliation, chemotherapy may be helpful
- the more proximal to the liver, the worse the prognosis
- overall 5 yr survival: 15%

Pancreas

Acute Pancreatitis

• see Gastroenterology, G45

GALLSTONE PANCREATITIS (35% of acute pancreatitis)

Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (pancreatitis of any etiology)
- pain (epigastric pain radiating to back), N/V, ileus, peritoneal signs, jaundice, fever
- Inglefingar’s sign: pain worse when supine, better when sitting forward
- rarely may have existent cholangitis or pancreatic necrosis
- Ranson’s criteria for determining prognosis of acute pancreatitis (see sidebar)
- physical exam may show: tachypnea, tachycardia, hypotension, abdominal distention and tenderness, Cullen’s sign, Gray Turner’s sign

Investigations
- high amylase (higher than alcoholic pancreatitis), lipase, leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), edematous pancreas
- CXR, AXR, CT (if severe to evaluate for complications)

Treatment
- supportive: e.g. NPO, hydration, analgesia, early enteric nutrition
- antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if failure of conservative management if stone impacted in CBD (benefits of early ERCP controversial)
- early ERCP if concomitant cholangitis
- surgical indications in acute pancreatitis (rare)
  - debridement and drain placement for necrotizing pancreatitis if refractory to medical management, if septic or in ICU without other sources of sepsis

Complications
- pseudocyst (collection of pancreatic secretions >4 wk old surrounded by a defined wall of granulation tissue)
- abscess/infection, necrosis
- splenic/mesenteric/portal vessel thrombosis or rupture
- pancreatic ascites/pancreatic pleural effusion
- DM
- ARDS/sepsis/multiorgan failure
- coagulopathy/DIC
- encephalopathy
- severe hypocalcemia
Chronic Pancreatitis

• see Gastroenterology, G47

Surgical Treatment
• treatment is generally medical
• indications for surgery
  • failure of medical treatment
  • debilitating abdominal pain
  • pseudocyst complications: persistence, hemorrhage, infection, rupture
  • CBD obstruction (e.g. strictures), duodenal obstruction
  • pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  • rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  • anatomical abnormality causing recurrent pancreatitis
• pre-operative CT and/or ERCP are mandatory to delineate anatomy
• minimally invasive options
  • endoscopic pancreatic duct decompression: less effective than surgery
  • extracorporeal shockwave lithotripsy: if pancreatic duct stones
  • celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery
• surgical options
  • drainage procedures: only effective if ductal system is dilated
    • Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
    • pancreaticojejunostomy: best option in absence of dilated duct
  • proximal disease: Whipple procedure (pancreatoduodenectomy) – pain relief in 80%
  • distal disease: distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy
  • total pancreatectomy: refractory disease
  • denervation of celiac ganglion and splanchnic nerves

PSEUDOCYST
• localized fluid collections rich in pancreatic enzymes, with a non-epithelialized wall consisting of fibrous and granulation tissue
• complication of chronic and/or acute pancreatitis
• often resolve spontaneously
• cyst wall must be mature prior to drainage (4-6 wk)
• pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first

Treatment
• surgical drainage (gold standard)
  • cystgastrostomy
  • cystenterostomy
  • resection
• endoscopic drainage
  • cystgastrostomy
  • cystduodenostomy
  • percutaneous catheter drainage
• consider biopsy of cyst wall to rule out cystadenocarcinoma

Pancreatic Cancer

Epidemiology
• fourth most common cause of cancer-related mortality in both men and women in Canada
• M:F = 1.3:1, average age: 50-70

Risk Factors
• increased age
• smoking: 2-5x increased risk, most clearly established risk factor
• high fat/low fiber diets, heavy alcohol use
• obesity
• DM, chronic pancreatitis
• partial gastrectomy, cholecystectomy
• chemicals: betanaphthylamine, benzidine
• African descent

Clinical Features
• head of the pancreas (70%)
  • weight loss, obstructive jaundice, steatorrhea, vague constant mid-epigastric pain (often worse at night, may radiate to back)
  • painless jaundice (occurs more often with peri-ampullary), Courvoisier’s sign (see sidebar GS49)
• body or tail of pancreas (30%)
  • tends to present later and usually inoperable
  • weight loss, vague mid-epigastric pain
  • <10% jaundiced
  • sudden onset DM
Investigations
- serum chemistry is non-specific, can have elevated ALP and bilirubin >300 µmol/L
- CA 19-9 (most useful serum marker of pancreatic cancer)
- U/S, contrast CT (also evaluates metastasis and resectability), ERCP, MRI, MRCP

Pathology
- ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- intraductal papillary mucinous neoplasm (IPMN)
- other: pancreatic neuroendocrine tumors (non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma), mucinous cystic neoplasm (MCN), acinar cell carcinoma,
  - see Surgical Endocrinology, GS60 for functional pancreatic neuroendocrine tumors

Treatment
- resectable (10-20% of pancreatic cancer)
  - no involvement of liver, peritoneum, or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreaticoduodenectomy) for cure <5% mortality
  - distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas
- borderline resectable
  - tumors that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
  - non-resectable (palliative ± relieve pain, obstruction)
  - most body/tail tumors are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
  - chemotherapy (gemcitabine, 5-FU), radiotherapy – only slightly increase survival

Prognosis
- most important prognostic indicators are lymph node status, margin status, size >3 cm, perineural invasion (invasion of tumor into microscopic nerves of pancreas)
- overall 5 yr survival for all patients with pancreas cancer is 1%; following surgical resection 5 yr survival is 20%
- median survival for unresectable disease: 3-6 mo if metastatic, 8-12 mo if locally advanced at presentation

### Table 20. TNM Classification System for Exocrine and Endocrine Tumors of the Pancreas

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX</td>
<td>M0</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tis</td>
<td>N1</td>
<td>M1</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to pancreas, &lt;2 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to pancreas, &gt;2 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends beyond pancreas, no involvement of celiac axis or superior mesenteric artery</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves celiac axis or superior mesenteric artery (unresectable)</td>
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### Table 21. Staging and Treatment of Pancreatic Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>5-Yr Survival</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
<td>14%</td>
<td>Surgical resection ± chemotherapy</td>
</tr>
<tr>
<td>IA</td>
<td>T1, N0, M0</td>
<td>14%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IB</td>
<td>T2, N0, M0</td>
<td>12%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIA</td>
<td>T3, N0, M0</td>
<td>7%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIB</td>
<td>T1-3, N1, M0</td>
<td>5%</td>
<td>Same as above</td>
</tr>
<tr>
<td>III</td>
<td>T4, any N, M0</td>
<td>3%</td>
<td>Borderline resectable, trial of chemotherapy and radiation</td>
</tr>
<tr>
<td>IV</td>
<td>any T, any N, M1</td>
<td>1%</td>
<td>Non-resectable, palliative treatments</td>
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</tr>
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<td>14%</td>
<td>Same as above</td>
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<td>1%</td>
<td>Non-resectable, palliative treatments</td>
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Spleen

Splenic Trauma

- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr’s sign

Treatment

- non-operative
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
  - partial splenectomy, rarely performed due to risk of recurrent hemorrhage
  - total splenectomy if patient unstable or high-grade injury

Splenectomy

Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenic purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenic purpura (TTP), sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIg

Complications

- short-term
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas)
  - post-operative thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk in those <16 yr old)
    - 50% mortality
    - prophylaxis with vaccinations, ideally 2 wk pre- or post-operative (pneumococcal, H. influenzae, and meningococcus)
    - liberal use of penicillin especially in children <6 yr old
    - splenosis: intra-abdominal “seeding” of splenic tissue during removal

Kehr’s Sign
Left shoulder pain due to diaphragmatic irritation from splenic rupture, worsens with inspiration

Indication of Splenectomy

SHIRTS
Splen ic abscess/splenomegaly
Hereditary spherocytosis
Immune thrombocytopenic purpura
Rupture of spleen
Thrombotic thrombocytopenic purpura
Splenic vein thrombosis
**Benign Breast Lesions**

**NON-PROLIFERATIVE LESIONS**
- also known as fibrocystic change, chronic cystic mastitis, mammary dysplasia
- benign breast condition characterized by fibrous and cystic changes in the breast
- no increased risk of breast cancer
- age 30 to menopause (and after if HRT used)
  - clinical features
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, nipple discharge (straw-like, brown, or green)
- treatment
  - evaluation of breast mass and reassurance
  - if >40 yr old: mammography every 3 yr
  - no strong evidence for avoidance of xanthine-containing products (coffee, tea, chocolate, cola)
  - analgesia (ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

**PROLIFERATIVE LESIONS – No Atypia**

**Fibroadenoma**
- most common benign breast tumor in women <30 yr
- risk of subsequent breast cancer is increased only if fibroadenoma is complex, there is adjacent atypia, or a strong family history of breast cancer
- clinical features
  - nodules: smooth, rubbery, discrete, well-circumscribed, non-tender, mobile, hormone-dependent
  - unlike cysts, needle aspiration yields no fluid
- investigations
  - core or excisional biopsy required
  - U/S and FNA alone cannot differentiate fibroadenoma from Phyllodes tumor
- treatment
  - generally conservative: serial observation
  - consider excision if size 2-3 cm and growing on serial U/S (q6mo x 2 yr is usual follow-up), if symptomatic, formed after age 35, or patient preference

**Intraductal Papilloma**
- solitary intraductal benign polyp
- present as nipple discharge (most common cause of spontaneous, unilateral, bloody nipple discharge), breast mass, nodule on U/S
- can harbor areas of atypia or DCIS
- treatment: excision of involved duct to ensure no atypia

**DDx for Breast Mass**

**Benign**
- Fibrocystic changes
- Fibroepithelial lesions (fibroadenoma most common; benign phyllodes also)
- Fat necrosis
- Papilloma/papillomatosis
- Galactoceles
- Duct ectasia
- Ductal/lobular hyperplasia
- Sclerosing adenosis
- Lipoma
- Neurofibroma
- Granulomatous mastitis (e.g. TB, granulomatosis with polyangiitis, sarcoidosis)
- Abscess
- Silicone implant

**Malignant**
- Breast cancer (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)
Ductal Hyperplasia Without Atypia
• increased number of cells within the ductal space
• cells retain benign cytology
• no treatment required
• slightly increased cancer risk if moderate or florid hyperplasia

PROLIFERATIVE LESIONS – With Atypia

Atypical Hyperplasias
• can involve ducts (ductal hyperplasia with atypia) or lobules (lobular hyperplasia with atypia)
• cells lose apical-basal orientation
• increased risk of breast cancer
• diagnosis: core or excisional biopsy
• treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

OTHER LESIONS

Fat Necrosis
• uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
• firm, ill-defined mass with skin or nipple retraction, ± tenderness
• regresses spontaneously, but complete imaging ± biopsy to rule out carcinoma

Mammary Duct Ectasia
• obstruction of a subareolar duct leading to duct dilation, inflammation, and fibrosis
• may present with nipple discharge, bluish mass under nipple, local pain
• risk of secondary infection (abscess, mastitis)
• resolves spontaneously

Montgomery Tubercle
• Montgomery tubercles (or Morgagni tubercles) are papular projections at the edge of the areola
• obstruction of these glands can lead to inflammation or cystic collections (cyst of Montgomery i.e. retroareolar cyst)
• if signs of secondary infection, start treatment for mastitis
• resolves spontaneously in weeks to years

Abscess
• lactational (see Obstetrics, OB49) vs. periductal/subareolar
• unilateral localized pain, tenderness, erythema, subareolar mass, nipple discharge, nipple inversion
• rule out inflammatory carcinoma, as indicated
• treatment: initially broad-spectrum antibiotics and I&D, if persistent total duct excision (definitive)
• if mass does not resolve: U/S to assess for presence of abscess, core biopsy to exclude cancer, consider MRI

Breast Cancer

Epidemiology
• 2nd leading cause of cancer mortality in women (1st is lung cancer)

Risk Factors
• gender (99% female)
• age (80% >40 yr)
• important risk factors are prior history of breast cancer and/or prior breast biopsy (regardless of pathology)
• 1st degree relative with breast cancer (greater risk if relative was premenopausal)
• increased risk with high breast density, nulliparity, first pregnancy >30 yr, menarche <12 yr, menopause >55 yr
• decreased risk with lactation, early menopause, early childbirth
• radiation exposure (e.g. mantle radiation for Hodgkin’s disease)
• >5 yr HRT
Investigations
- mammography
  - indication
    - screening, see Family Medicine, FM4
    - findings indicative of malignancy
      - mass that is poorly defined, spiculated border
      - microcalcifications
      - architectural distortion
      - interval mammographic changes
      - normal mammogram does not rule out suspicion of cancer based on clinical findings
  - other radiographic studies
    - U/S: differentiate between cystic and solid
    - MRI: high sensitivity, low specificity
    - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
    - metastatic workup as indicated (usually after surgery or if clinical suspicion of metastatic disease): bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), CT head (only if specific neurological symptoms)

Diagnostic Procedures
- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- fine needle aspiration (FNA): for palpable solid masses; need experienced practitioner for adequate sampling
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

Genetic Screening
- consider testing for BRCA1/2 if:
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer
  - young patient (<35 yr)
  - bilateral breast cancer in patients <50 yr

Staging
- clinical
  - tumor size by palpation, mammogram
  - nodal involvement by palpation
  - metastasis by physical exam, CXR, and abdominal U/S (or CT chest/abdomen/pelvis), bone scan (usually done post-operative if node-positive disease)
- pathological
  - tumor size
    - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear, and mitotic grade
    - number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, sentinel node positive/negative
    - estrogen receptor (ER) + progesterone receptor (PR) testing
    - Her2Neu receptor testing
    - margins: negative, <1 mm, positive
    - lymphovascular invasion (LVI)
    - extensive in situ component (EIC): DCIS in surrounding tissue
    - involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

Table 22. Staging of Breast Cancer (American Joint Committee on Cancer)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Nodes (regional) (clinical)</th>
<th>Metastasis</th>
<th>Survival (5 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>in situ</td>
<td>None</td>
<td>None</td>
<td>99%</td>
</tr>
<tr>
<td>I</td>
<td>&lt;2 cm</td>
<td>None</td>
<td>None</td>
<td>94%</td>
</tr>
<tr>
<td>II A</td>
<td>&lt;2 cm</td>
<td>Mobile ipsilateral</td>
<td>None</td>
<td>85%</td>
</tr>
<tr>
<td>II B</td>
<td>2-5 cm</td>
<td>None or mobile ipsilateral</td>
<td>None</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>or &gt;5 cm</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>III A</td>
<td>Any size</td>
<td>Fixed ipsilateral or internal mammary</td>
<td>None</td>
<td>52%</td>
</tr>
<tr>
<td>III B</td>
<td>Skin/chest wall invasion</td>
<td>Any</td>
<td>None</td>
<td>48%</td>
</tr>
<tr>
<td>III C</td>
<td>Any size</td>
<td>Ipsilateral infraclavicular/internal mammary plus axillary nodes; ipsilateral supraclavicular node(s) ± axillary nodes</td>
<td>None</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>Distant</td>
<td>18%</td>
</tr>
</tbody>
</table>

Favorable Features
- <2 cm
- Grade I (low grade)
- Node negative
- ER positive
- Mucinous pattern

Unfavorable Features
- >5 cm
- Grade III (high grade)
- Node positive
- ER negative
- Inflammatory cancer
- Her2Neu positive
- Positive margins
- UV
- EIC
- Dermal lymphatics involved

Phyllodes tumors are rare fibroepithelial breast tumors that can be benign or malignant that mostly affect women from 35-55 yr

Any palpable dominant breast mass requires further investigation

Diagnostic mammography is indicated in all patients, even in women <50 yr
Pathology

- non-invasive (cannot penetrate basement membrane)
  - ductal carcinoma in situ (DCIS)
    - proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
    - 80% non-palpable, detected by screening mammogram
    - risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
  - treatment
    - lumpectomy with wide excision margins + radiation (5-10% risk invasive cancer)
    - mastectomy if large area of disease, high grade, or multifocal (risk of invasive cancer reduced to 1%)
    - possibly tamoxifen as an adjuvant treatment
    - 99% 5 yr survival
- lobular carcinoma in situ (LCIS)
  - neoplastic cells completely contained within breast lobule
  - no palpable mass, no mammographic findings, usually incidental finding on breast biopsy for another indication
  - treatment
    - clinical follow-up
    - chemoprevention (tamoxifen)
    - surgery (uncommon)
  - not a precursor lesion, but considered a risk factor for breast cancer development
- invasive
  - invasive ductal carcinoma (most common 80%)
    - originates from ductal epithelium and infiltrates supporting stroma
    - characteristics: hard, scirrhus, infiltrating tentacles, gritty on cross-section
  - invasive lobular carcinoma (8-15%)
    - originates from lobular epithelium
    - 20% bilateral (i.e. more often than infiltrating duct carcinoma)
    - does not form microcalcifications, harder to detect mammographically (may benefit from MRI)
  - Paget’s disease (1-3%)
    - ductal carcinoma that invades nipple with scaling, eczematoid lesion
  - inflammatory carcinoma (1-4%)
    - ductal carcinoma that invades dermal lymphatics
    - most aggressive form of breast cancer
    - clinical features: erythema, skin edema, warm, swollen and tender breast ± lump
    - peau d’orange indicates advanced disease (IIIb-IV)
  - male breast cancer (<1%)
    - most commonly invasive ductal carcinoma
    - often diagnosed at later stages
    - stage-for-stage similar prognosis to breast cancer in females
    - consider genetic testing
  - sarcomas: rare
    - most commonly Phyllodes tumor, a variant of fibroadenoma with potential for malignancy
    - can also be angiosarcomas – after previous radiation
  - lymphoma: rare
  - other: papillary, medullary, mucinous, tubular cancers
  - generally better prognosis

Treatment

Table 23. Breast Cancer Treatment by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Treatment Options</th>
<th>Adjuvant Systemic Therapy</th>
</tr>
</thead>
</table>
| 0 (in situ) | BCS + radiotherapy  
BCS alone if margins > 1 cm and low nuclear grade  
Mastectomy* ± SLNB       | None                                      |
| I       | BCS + axillary node dissection + radiotherapy  
Mastectomy* ± axillary node dissection/SLNB       | May not be needed; discuss risks/benefits of chemotherapy and tamoxifen |
| II      | BCS + axillary node dissection + radiotherapy  
Mastectomy* ± axillary node dissection/SLNB       | Chemotherapy for premenopausal women or postmenopausal and estrogen receptor (ER) negative, followed by tamoxifen if ER positive |
| III     | Likely mastectomy + axillary node dissection + radiotherapy       | Neoadjuvant therapy may be considered i.e. pre-operative chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-operative) |
| Inflammatory | Likely mastectomy + axillary node dissection + radiotherapy       | Neoadjuvant therapy                      |
| IV      | Surgery as appropriate for local control   | Primary treatment is systemic therapy i.e. chemotherapy and/or hormone therapy |

BCS = breast-conserving surgery; SLNB = sentinel lymph node biopsy

*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient’s preference since choice of local treatment does not significantly affect survival if local control is achieved
Primary Surgical Treatment

- **BCS:** lumpectomy with wide local excision
  - for treatment of stage I and II disease
  - must be combined with radiation for survival equivalent to mastectomy
- **contraindications**
  - high risk of local recurrence: extensive malignant-type calcifications on mammogram, multifocal primary tumors, or failure to obtain tumor-free margins after re-excision
  - contraindications to radiation therapy (pregnancy, previous radiation, collagen vascular disease)
  - large tumor size relative to breast
- **mastectomy**
  - radical mastectomy (rarely done anymore): removes all breast tissue, skin, pectoralis muscle, axillary nodes
  - modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
  - simple mastectomy: removes all breast tissue and skin
  - see Plastic Surgery, PL32 for breast reconstruction
- **axillary lymph node dissection (ALND)**
  - performed if SLNB is positive or nodes are clinically concerning
  - risk of arm lymphedema (10-15%), decreased arm sensation, shoulder pain
- **sentinel lymph node biopsy (SLNB)**
  - technetium-99 ± blue dye injected at tumor site prior to surgery to identify sentinel node(s)
  - intraoperative frozen section
  - proceed with ALND if positive
  - 5% false negative rate

Adjuvant/Neoadjuvant

- **radiation**
  - indications
    - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy (if >4 nodes positive or tumor >5 cm)
    - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement
- **hormonal**
  - indications
    - ER positive plus node-positive or high-risk node-negative
    - tamoxifen if premenopausal or aromatase inhibitors (e.g. anastrozole)
    - ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), androgens (e.g. fluoxymesterone) are other options
- **chemotherapy**
  - indications
    - ER negative plus node-positive or high-risk node-negative
    - stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
    - palliation for metastatic disease

Post-Treatment Follow-Up

- visits q3-6mo x 2 yr and annually thereafter (frequency is controversial)
- annual mammography; no other imaging unless clinically indicated
- psychosocial support and counseling

Local/Regional Recurrence

- recurrence in treated breast or ipsilateral axilla
- 1% per year up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis

- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation
Surgical Endocrinology

Thyroid and Parathyroid

• see Endocrinology, E20 and Otolaryngology, OT35-OT38

Thyroidectomy

• indications: thyroid cancer, symptomatic thyroid mass or goiter, medically refractory Graves' or hyperthyroidism
• contraindications: uncontrolled severe hyperthyroidism (i.e. Graves') due to risk of intraoperative or post-operative thyroid storm
• pre-operative workup: thyroid U/S for thyroid nodules, FNA for large nodules, U/S of the neck for lesions suspicious for papillary or medullary thyroid cancer, CT neck useful to rule out extension, vocal cord function
• complications: hypocalcemia secondary to hypoparathyroidism, recurrent/superior laryngeal nerve injury, neck hematoma, infection, thyrotoxic storm

Parathyroidectomy

• indications: symptomatic primary hyperparathyroidism due to effects of PTH on bone or kidneys, asymptomatic primary hyperparathyroidism with specific laboratory criteria (elevated serum Ca, marked hypercalciuria, Cr clearance <30% normal, bone density reduction with T score <2.5, age <50 yr)
• contraindications: familial hypocalciuric hypercalcemia
• pre-operative workup: 99mTc sestamibi scanning, ± SPECT or CT, U/S
• complications: recurrent/superior laryngeal nerve injury, post-operative hypocalcemia, infection, bleeding

Adrenal Gland

• see Endocrinology, E29
• functional anatomy
  ▪ cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), reticularis (sex steroids)
  ▪ medulla: catecholamines (epinephrine, norepinephrine)
• types of adrenal tumors: functional (e.g. Cushing's syndrome, Conn's syndrome) or non-functional

INCIDENTALOMA

• adrenal mass discovered by investigation of unrelated symptoms

Epidemiology

• benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
• metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, kidney
• peak incidence of carcinoma: females age 50-60, risk decreases with increasing age and male gender

Investigations

• MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
• functional studies
  ▪ pheochromocytoma: 24 h urine epinephrine, norepinephrine, metanephrine, normetanephrine, VMA (vanillylmandelic acid)
  ▪ Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  ▪ aldosteronoma: electrolytes, aldosterone:renin level, saline suppression test if appropriate
  ▪ adrenal androgens: 17-ÖH progesterone, DHEAS
• FNA biopsy: if suspect metastasis to adrenal (must exclude pheochromocytoma first to prevent a hypertensive crisis)
• indicated if history of cancer or patient is smoker
• iodocholesterol scintigraphy: may distinguish benign vs. malignant disease

Treatment

• functional tumor: resect
• non-functional tumor
  ▪ >4 cm: resect
  ▪ <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement
INSULINOMA
• tumor that secretes insulin
• most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

Clinical Features
• Whipple's triad
  • palpitations, trembling, diaphoresis, confusion, seizure, personality changes

Investigations
• blood work: decreased serum glucose and increased serum insulin and C-peptide
• U/S, CT: insulinomas evenly distributed throughout head, body, tail of pancreas

Treatment
• only 10% are malignant
• enucleation of solitary insulinomas may be done endoscopically
• tumors >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

GASTRINOMA
• tumor secreting gastrin; cause of Zollinger-Ellison syndrome

Clinical Features
• abdominal pain, PUD, severe esophagitis
• multiple ulcers in atypical locations refractory of antacid therapy

Investigations
• blood work: serum gastrin levels (usually >1,000 pg/mL), secretin stimulation test
• U/S, CT: 70-90% found in Passaro's triangle (head of pancreas medially, 2nd portion of duodenum inferiorly, and the confluence of the cystic and CBD superiorly)
• octreotide scintigraphy scan

Treatment
• 50% are malignant
• surgical resection of tumor dependent on location
• non-surgical treatment: chemotherapy, somatostatin analogues, interferon, chemoembolization
• if inoperable, vagotomy can be performed for symptomatic control

VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOR
• tumor secreting VIP; commonly located in the distal pancreas and most are malignant when diagnosed

Clinical Features
• severe watery diarrhea causing dehydration, weakness, electrolyte imbalance

Investigations
• blood work: serum VIP levels
• U/S, CT

Treatment
• somatostatin analogues
• surgical resection/palliative debulking
# Pediatric Surgery

## Table 24. Pediatric Surgery

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<tr>
<td><strong>Hydrocele (see Urology, U28)</strong></td>
<td>1-2% of live births  Present at birth, majority close spontaneously by 1 yr  M:F = 6:1  Prematurity</td>
<td><strong>Communicating hydroceles</strong>: processus vaginalis fails to close with small opening for fluid to move freely between peritoneal cavity through patent processus (if opening progresses to allow passage of intestine, it is a hernia)</td>
<td>Painless scrotal mass  Communicating hydroceles increase in size with standing or Valsalva, may be absent in the morning and large in the evening</td>
<td>Transillumination suggests hydrocele  Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk</td>
<td>U/S if suspect pathology</td>
<td>Most resolve spontaneously by 1 yr  Surgical repair if:  – Persistence &gt;2 yr  – Pain  – Fluctuating in size which suggests communication  – Cosmetic reasons  – Infection</td>
<td>&lt;2% recurrence</td>
</tr>
<tr>
<td><strong>Hypertrophic Pyloric Stenosis</strong></td>
<td>0.03-1.0% of live births  Can present at 1-20 wk, most commonly at 6-8 wk  M:F = 4:1  Early erythromycin exposure (&lt;13 d old)</td>
<td>Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction  Hypovolemia caused by emesis of gastric contents causes hyperchloremic metabolic alkalosis  Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria</td>
<td>Projectile non-bilious vomiting  Vomiting 30-60 min after feeds  Hangry after vomiting  Dehydration (variable severity)</td>
<td>Smooth oblong 1-2 cm mass palpable above umbilicus, “olive”  Visible left-to-right gastric contraction “waves” after feeding</td>
<td>Electrolytes (assess hypochloremia, dehydration)  U/S shows pyloric length &gt;14 mm, muscle thickness &gt;4 mm  Upper GI series necessary only when U/S unavailable or non-diagnostic will show “string sign”</td>
<td>Fluid reuscitate with normal saline, correct electrolyte and acid-base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate  NGT decompression unnecessary  Pyloromyotomy, open (Flamstedt vs. transumbilical or laparoscopic approach)  Alternative therapies such as TPN/wat or atroine impractical due to long time course of effect</td>
<td>Pyloromyotomy curative</td>
</tr>
<tr>
<td><strong>Congenital Diaphragmatic Hernias</strong></td>
<td>1 in 2,000 to 5,000 live births  Presents within hours of life although some cases of delayed presentation  M:F = 10% are associated with other congenital anomalies  Prenatal diagnosis common</td>
<td><strong>Left-sided</strong>: small bowel, large bowel, stomach, and solid visera (spleen, left lobe of liver) herniate into thorax  <strong>Right-sided</strong>: liver, large bowel herniate into thorax  Pulmonary hypoplasia  Pulmonary HTN  Early respiratory distress  Cyanosis  Scaphoid abdomen  Prenatal diagnosis  Decreased air entry ± bowel sounds in the chest  Displaced heart sounds  Echocardiography  Genetic consultation if warranted</td>
<td>Intubate  Orogastric suction  Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extracorporeal membrane oxygenation)  Surgical repair after stable by hernia reduction and closure of diaphragmatic defect – open vs. thoracoscopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect  Later presentations have better outcomes  Hearing deficit (40%)  Associated Gerd  MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy</td>
<td>Later presentations have better outcomes  Hearing deficit (40%)  Associated Gerd  MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy</td>
<td>Later presentations have better outcomes  Hearing deficit (40%)  Associated Gerd  MSK defects – chest wall and scoliotic defects a potential complication of thoracotomy</td>
<td>Need for long-term surveillance for potential recurrence  Failure to thrive  Chronic lung disease if severe hypoplasia</td>
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[Hypertrophic Pyloric Stenosis](#)  
Non-bilious emesis in infant is the classic presentation
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<tr>
<td><strong>Meckel’s Diverticulum</strong>&lt;br&gt;Most common remnant of vitelline duct that connects yolk sac with primitive midgut</td>
<td>1:3% of population&lt;br&gt;M/F = 2:1&lt;br&gt;Present most frequently during first 5 yr of life&lt;br&gt;Symptomatic in 2% of cases</td>
<td>Failure of vitelline duct to regress 5-7 wk in utero; 30% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphaloemiserentric fistula, umbilical sinus, umbilical cyst, fibrous band</td>
<td>BRBPR (heterotopic gastric mucosa in Meckel’s causing mucosal ulceration and bleeding in adjacent small bowel mucosa)&lt;br&gt;Abdominal sepsis (Meckel’s diverticulitis ± perforation)&lt;br&gt;Small bowel volvulus around fibrous band</td>
<td>Tenderness (lower abdomen) near umbilicus</td>
<td>AXR: Meckel scan; scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 85%, specificity 95%)</td>
<td>Stabilize, resection by laparotomy or laparoscopy ± incidental appendectomy</td>
<td>Resection curative</td>
</tr>
<tr>
<td><strong>Malrotation</strong>&lt;br&gt;1:500 live births&lt;br&gt;1/3 present by 1 wk of age, 3/4 by 1 mo of age, 90% by 1 yr of age&lt;br&gt;M:F = 1:1; higher incidence among patients with cardiac anomalies, heterotaxy syndromes</td>
<td>Failure of gut to normally rotate around SMA with associated abnormal intestinal attachments and anatomic positions&lt;br&gt;Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high risk for volvulus)</td>
<td>Bilious emesis is THE cardinal sign, especially if abdomen nondistended&lt;br&gt;If bilious emesis in ill child with distended abdomen, consider surgical exploration to rule out volvulus&lt;br&gt;Rectal bleed (late/ ominous sign) Intermittent symptoms</td>
<td>Bilious drainage from NGT&lt;br&gt;Tachycardic, pale&lt;br&gt;Diaphoretic&lt;br&gt;Flat abdomen</td>
<td>AXR: obstruction of proximal small bowel, double-bubble sign, intestinal wall thickened&lt;br&gt;Immediate UGI: dilated duodenum, duodenojejunal segment (Ligament of Treitz) right of midline and not fixed posteriorly over spinal column, “corkscrew” sign indicating volvulus&lt;br&gt;U/S: “whirlpool” sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies</td>
<td>IV antibiotics&lt;br&gt;Fluid resuscitation&lt;br&gt;EMERGENT LAPAROTOMY&lt;br&gt;Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd’s bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide congenital adhesions), ± appendectomy&lt;br&gt;Positioning the bowel into non-rotation (small bowel in right abdomen, large bowel in left abdomen)</td>
<td>Mortality related to length of bowel loss: 10% necrosis – 100% survival rate, 75% necrosis – 35% survival rate&lt;br&gt;Recurrence 2-6%</td>
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<tr>
<td><strong>Gastrochisis</strong>&lt;br&gt;1:2,000 live births&lt;br&gt;Antenatal diagnosis common&lt;br&gt;Increased with younger maternal age and associated with EUR&lt;br&gt;M/F = 1:1</td>
<td>Defect of abdominal wall, with free extrusion of intestine into amniotic cavity&lt;br&gt;No specific environmental factor identified&lt;br&gt;Defect in embryogenesis unclear</td>
<td>Not associated with genetic syndromes&lt;br&gt;10% with intestinal atresia&lt;br&gt;Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of hemirotated bowel</td>
<td>Hollow viscera (stomach, small and large bowels)&lt;br&gt;Defect lateral to cord (usually right)&lt;br&gt;Bowel may be inflamed, thickened, matted, foreshortened&lt;br&gt;Defect size variable</td>
<td>Pranatal U/S&lt;br&gt;Elevated MS-AFP&lt;br&gt;NGT decompression&lt;br&gt;IV fluids&lt;br&gt;IV antibiotics&lt;br&gt;Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo&lt;br&gt;May have bowel dysmotility requiring motility medications</td>
<td>&gt;90% survival rate</td>
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<tr>
<td><strong>Omphalocele</strong>&lt;br&gt;1:5,000 live birth&lt;br&gt;Antenatal diagnosis common&lt;br&gt;Lower gestational age&lt;br&gt;Increased maternal age&lt;br&gt;M/F = 1.5:1</td>
<td>Defect of abdominal wall, with extrusion of sac covered viscera (ammon, Wharton’s jelly, peritoneum)&lt;br&gt;Duhameel’s theory – failure of body wall morphogenesis</td>
<td>Associated with genetic syndromes 30-70% (e.g. Pentolagy of Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome)&lt;br&gt;Associated pulmonary hypoplasia</td>
<td>Hollow viscera (stomach, small and large bowels, often liver)&lt;br&gt;Cord on the sac</td>
<td>Pranatal U/S&lt;br&gt;Elevated MS-AFP&lt;br&gt;NGT decompression&lt;br&gt;IV fluids&lt;br&gt;IV antibiotics&lt;br&gt;Small defect (&lt;2 cm): Primary closure&lt;br&gt;Medium (2-4 cm) and large (&gt;4 cm) defects best treated with silver sulfadiazine to promote epithelialization coupled with compression dressing to allow gradual reduction, followed by future repair with or without mesh</td>
<td>40-70% survival rate&lt;br&gt;Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles</td>
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Bilious vomitting in infant is a life-threatening emergency secondary to midgut volvulus until proven otherwise

Rule of 2s for Meckel’s Diverticulum
- 2% of the population
- 2:1 male-to-female ratio
- Symptomatic in 2% of cases
- Found within 2 feet (10-90 cm) of the ileocecal (IC) valve
- 2 inches in length
- 2 inches in diameter
- 2 types of tissue (gastric, pancreatic)
- Often present by 2 yr of age
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<tr>
<td>Umbilical Hernias</td>
<td>Incidence 2-14% Increases with prematurity Decreases with increasing age</td>
<td>Incomplete closure of peritoneal and fascial layers within umbilicus by 5 yr</td>
<td>Majority asymptomatic Majority spontaneously resolve by age 5 Incarceration prior to age 5 very rare Most symptoms occur in late adolescence or adulthood</td>
<td>Protrusion from umbilicus Important to differentiate from less common abdominal wall hernias that do not spontaneously resolve (e.g. epigastric hernias) Most umbilical fascial defects &gt;1.5 cm in infancy will not close spontaneously</td>
<td>None if uncomplicated</td>
<td>Repair if not spontaneously closed by age 5 Earlier repair of large “proboscis” hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect</td>
<td>Low risk of recurrence</td>
</tr>
<tr>
<td>Intestinal Atresia</td>
<td>Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or “double-bubble” sign on x-ray for duodenal atresia Decreasing with increasing age</td>
<td>Duodenal – failure of bowel to recanalize after endodermal epithelium proliferation wk (8-10) Jejunal/ileal – acquired as a result of vascular disruption → ischemic necrosis → resorption of necrotic tissue → blind distal and proximal ends Colonic – mechanism unknown, thought to be similar to small bowel atresia</td>
<td>Gastric distension and vomiting (usually bilious) Duodenal – may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal, and vertebral anomalies), 24-28% have Down syndrome Jejunal/ileal – within 2 d of birth, may be associated with CF Colonic – within 3 d of birth</td>
<td>Complete physical Special attention to abdominal exam Peritoneum and anus Include evaluation of respiratory distress and signs of volume depletion Congenital anomalies Jaundice</td>
<td>Contrast enema ± UGI with small bowel follow through (SBFT) Group and screen INR and PTT if for surgery</td>
<td>NPD NBT decompression Fluid resuscitate TPN Broad spectrum antibiotics Duodenal – duodenoduodenostomy or duodenoenjejunostomy Jejunal/ileal – primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures Colonic – primary anastomosis</td>
<td>Long-term survival Duodenal – 86% Jejunal/ileal – 84% Colonic – 100%</td>
</tr>
<tr>
<td>Hirschsprung’s Disease</td>
<td>1.5,000 births M:F = 3.1 to 4:1 approaches 1:1 when whole colon involved Can have aganglionosis of small bowel as well Familial Hirschsprung’s in &lt;5% of cases</td>
<td>Defect in migration of neurocrest cells to intestine resulting in aganglionic bowel that fails to peristalsate and internal sphincter that fails to relax (internal anal sphincter achalasia) causing functional and partial mechanical obstruction, respectively; always starts in the rectum and variable involvement proximally; RET mutation</td>
<td>Failure to pass meconium spontaneously within 48 h of life is the classic history (96% of normal children should pass meconium within 24 h, and the remaining 5% within 48 h) Symptoms of bowel obstruction: abdominal distension, constipation, bilious emesis Enterocolitis/sepis Failure to thrive</td>
<td>± abdominal distension Squirt/blast sign Rectal biopsy (gold standard) – look for aganglionosis and neurohypertrophy AXR Contrast enema to find narrow rectum and transition zone Anal manometry unreliable in infants – classic finding is absence of rectoanal inhibitory reflex</td>
<td>Surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis</td>
<td>Surgical resection of aganglionic intestinal segment and anastomosis of remaining intestine to anus Either in newborn period or staged if extensive aganglionosis</td>
<td>Most have normal/ near-normal anorectal function Complications: Fecal incontinence and constipation, post-operative enterocolitis (medical emergency if progresses to sepsis)</td>
</tr>
<tr>
<td>Cryptorchidism</td>
<td>2.5% of term males – most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend Idiopathic Descent is mediated by descendin which is created in response to testosterone Descent usually begins at 28 wk</td>
<td>Palpable testicle within inguinal canal or testicle which can be milked down into scrotum (called retractile tests) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities</td>
<td>Bi-annual testicular exam with palpation Distinguish truly undescended testis from retractile tests (which is “high” testis due to hyperactive cremasteric muscles)</td>
<td>Depends on age of presentation US or MRI if no palpable tests Older child: LH, FSH, MIS, hCG stimulation test for gonadotropin production Infant: US, FSH, LH, karyotype, MIS, 17-hydroxyprogesterone</td>
<td>hCG to stimulate testosterone production and descent Orchidopexy – especially if undescended by age 6 mo-2 yr</td>
<td>Orchidopexy Decreased risk of torsion and blunt trauma to testicle No effect on malignant potential of testicle Descent can preserve spermatogenesis if performed by 1 yr of age 1/1,000 risk for testicular cancer (population risk is 1/4,000)</td>
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### Table 24. Pediatric Surgery (continued)

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<tr>
<td>Inguinal Hernias</td>
<td>5% of all term newborns 2x risk and more likely bilateral if pre-term M:F = 4:1 Low birth weight increases risk 1/5 inguinal hernias will become incarcerated if patient is &lt; 1 yr old Incarceration is more common in females Associated with other conditions: androgen insensitivity, connective tissue diseases</td>
<td>All infant hernias are indirect: descent of intra-abdominal contents through the internal inguinal ring through a patent tunica vaginalis</td>
<td>Most common presentation: painless intermittent mass in groin, may also note extension into scrotum (scrotal mass in absence of inguinal mass is a hydrocele) If incarcerated: tender; vomiting, firm mass, erythema then cyanosis of mass may be noted</td>
<td>Palpate for “bag of worms” suggests possible testicular varicocele Biannual testicular exam + palpation along inguinal canal to evaluate for any masses “Silk sign” — palpable thickening of cord Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen Must always try reduction to confirm that hernia is not incarcerated</td>
<td>Physical exam is gold standard U/S only if physical exam uncertain (e.g. in small infants where exam can be difficult)</td>
<td>Manual reduction — to relieve acute symptoms Hemororhaphy — definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias Laparoscopic or open techniques</td>
<td>Risk of recurrence after surgical reduction &lt; 3% but higher if repair done in premature infants or if hernia was incarcerated/strangulated</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Most common cause of bowel obstruction between the ages of 6-36 mo 26/100,000 newborns M:F = 2:2 Pathologic lead points: enlarged Peyer’s patches due to viral infections of the GI tract, polypos, Meckel’s diverticulum CF, lymphoma, IBD may increase risk</td>
<td>Idiopathic is most common Usually starts at ileocecal junction Telescoping of bowel into itself causing an obstruction and vascular compromise</td>
<td>Acute onset of abdominal pain which is classic episodic “colicky” pain Vomiting = bilious Abdominal mass Current-jelly stool suggests mucosal necrosis and sloughing</td>
<td>Abdominal exam Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness Signs of bowel obstruction: distended abdomen Look for localized peritonitis which suggests transmural ischemia</td>
<td>AXR for signs of bowel obstruction or perforation U/S if suspect pathology</td>
<td>If peritonitis, then consider operative management Non-operative management involves reduction via air contrast enema Operative reduction can be done open or laparoscopically Resection of involved colon if failure to reduce or bowel appears compromised</td>
<td>10% recurrence rate If recurrent = more likely non-idiopathic In successfully reduced by enema in older children allow 2 wk resolution of edema then perform SBFT to rule out pathologic lead points</td>
</tr>
<tr>
<td>Tracheoesophageal Fistula (TEF)</td>
<td>Associated anomalies in 50%: VACTERL association (see Pediatrics: P42)</td>
<td>Varies with type of fistula May have history of maternal polyhydramnios May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds, respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth and nose that return after suctioning</td>
<td>X-ray: anatomic abnormalities, NGT curled in pouch</td>
<td>Investigate for other congenital anomalies, early repair by surgical ligation to prevent lung damage and maintain nutrition and growth</td>
<td>Complications: pneumonia, sepsis, reactive airways disease Following repair: esophageal stenosis and strictures at repair site, GERD, and poor swallowing (i.e. dysphagia, regurgitation)</td>
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### Skin Lesions

- see Dermatology, D5; Emergency Medicine, ER17; Plastic Surgery, PL5
Common Medications

Antiemetics
- dimenhydrinate (Gravol®) 25-50 mg PO/IM q4-h pm
- prochlorperazine (Stemetil®) 5-10 mg PO/IM bid-tid pm
- metoclopramide (Maxeran®) 10 mg IV/mq q2-3-h pm, 10-15 mg PO qid (30 min before meals and qhs)
- ondansetron (Zofran®) 4-8 mg PO q8-h pm
- granisetron (Kytril®) 1 mg PO bid (for nausea from chemotherapy/radiation)

Analgesics
- acetaminophen + codeine (Tylenol® #3/plain) 1-2 tabs q4-6-h PO/PR pm
- hydromorphone i+iv tabs PO q4-h pm, 0.5-2 mg IV q3-4-h pm
- ibuprofen 200-400 mg PO q4-h pm
- morphine 2.5-10 mg IM/SC q4-h pm + 1-2 mg IV q1-h pm for breakthrough
- ketorolac (Fortadol®) 30-60 mg IM/IV q6-h pm
- Percoct® (acetaminophen/oxycodeone, 325/5 mg) 1-2 tabs PO q4-h pm

DVT Prophylaxis
- heparin 5,000 units SC bid, if cancer patient then heparin 5,000 units SC tid
- dalfopristin (Fragmin®) 5,000 units SC daily
- enoxaparin (Lovenox®) 40 mg SC daily

Antidiarrheals
- loperamide (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d
- diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO qid

Laxatives
- sennosides (Senokot®) 1-2 tabs qhs
- docusate sodium (Colace®) 100 mg PO bid
- glycerine suppository 1 tab PR pm
- lactulose 15-30 mL PO qid pm
- milk of magnesia (MOM) 30-60 mL PO qid pm
- bisacodyl (Dulcolax®) 10-15 mg PO daily

Sedatives
- zopiclone (Imovane®) 5-7.5 mg PO qhs pm
- lorazepam (Ativan®) 0.5-2 mg PO/SL qhs pm

Antibiotics
- cefazolin (Ancef®) 1 g IV/IM on call to OR or q8-h – GP except Enterococcus, GN only E. coli, Klebsiella, and Proteus
- cefalexin (Keflex®) 250-500 mg PO qid – Listeria, GP except Enterococcus, GN only E. coli, Klebsiella, and Proteus
- ceftriaxone 1-2 g IV/mq q4-h – broad coverage including Pseudomonas
- ampicillin 1-2 g IV q4-h – Listeria, GP (Enterococcus) except Streplococcus and E. coli, oral anaerobes
- except Bacteroides
- gentamicin 3.5 mg/kg/d IV/IM divided q8-h; monitor creatinine, gentamicin levels – GN including Pseudomonas
- ciprofloxacin 400 mg IV q12-h, 500 mg PO bid – GN including Pseudomonas
- metronidazole (Flagyl®) 500 mg PO/IV bid (500 mg PO tid for C. difficile) – anaerobes
- clindamycin 600-900 mg IV q8-h, 150-400 mg PO qid – GP except Enterococcus, anaerobes
- piperacillin/tazobactam 4.5 mg IV q6-h – GP, GN, and anaerobes
- vancomycin 1g IV q2-h – GP and MRSA
- sulfamethoxazole/trimethoprim DS (Septra®) PO bid – GP, GN including noncardiac

Over-the-Counter Medications
- Pepso-Bismol® (bismuth subsalicylate) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d
- side effects: black stools, risk of Reyes’s syndrome in children
- Alka-Seltzer® (ASA + citrate + bicarbonate) 2 tabs in 4 oz water PO q4-h pm, max 8 tabs
- Maalox® (aluminum hydroxide + magnesium hydroxide) 10-20 mL or 1-4 tabs PO pm
- Tums® (calcium carbonate) 1-3 g PO q2-h pm
- Rolaid® (calcium carbonate and magnesium hydroxide) 2-4 tabs PO q1h pm, max 12 tabs/d

References
Seniors in the U.S.

Health Status

Table 1. Causes of Mortality and Morbidity in Canadian and American Seniors

<table>
<thead>
<tr>
<th>Mortality (U.S.)</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Diseases of the heart and circulatory system (27.0%)</td>
<td>1. HTN</td>
</tr>
<tr>
<td>2. Malignant neoplasms (22.0%)</td>
<td>2. Arthritis</td>
</tr>
<tr>
<td>3. Cerebrovascular disease (6.0%)</td>
<td>3. Heart disease</td>
</tr>
<tr>
<td>4. Chronic lower respiratory disease (7.0%)</td>
<td>4. Diabetes</td>
</tr>
<tr>
<td>5. Accidents (4.4%)</td>
<td>5. Ulcers</td>
</tr>
<tr>
<td>6. Alzheimer’s (5.0%)</td>
<td>6. Stroke</td>
</tr>
<tr>
<td></td>
<td>7. Asthma</td>
</tr>
<tr>
<td></td>
<td>8. Allergies</td>
</tr>
</tbody>
</table>

Death in the United States. NCHS Data Brief 2009;No64:2011

Physiology and Pathology of Aging

Definition

• major categories of impairment that appear with old age and affect the physical, mental, and social domains of the elderly, usually due to many predisposing and precipitating factors, rather than a single cause

Table 2. Changes Occurring Frequently with Aging

<table>
<thead>
<tr>
<th>System</th>
<th>Physiological Changes</th>
<th>Pathological Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Decreased wakefulness, brain mass, cerebral blood flow</td>
<td>Increased insomnia, neurodegenerative disease, stroke, decreased reflex response</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Decreased lacrimal gland secretion, lens transparency, dark adaptation, decreased sense of smell and taste</td>
<td>Increased glaucoma, cataracts, macular degeneration, presbycusis, presbyopia, tinnitus, vertigo, oral dryness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased sBP, dBP, decreased HR, CO</td>
<td>Increased atherosclerosis, CAD, MI, CHF, HTN, arrhythmias</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased tracheal cartilage calcification, mucous gland hypertrophy</td>
<td>Increased COPD, pneumonia, pulmonary embolism</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Increased intestinal villous atrophy, Decreased esophageal peristalsis, gastric acid secretion, liver mass, hepatic blood flow, calcium and iron absorption</td>
<td>Increased cancer, diverticulitis, constipation, fecal incontinence, hemorrhoids, intestinal obstruction</td>
</tr>
<tr>
<td>Renal and Urologic</td>
<td>Increased proteinuria, urinary frequency, Decreased renal mass, creatinine clearance, urine acidification, hydroxylation of vitamin D, bladder capacity</td>
<td>Increased urinary incontinence, nocturia, BPH, prostate cancer, pyelonephritis, nephrolithiasis, UTI</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Decreased androgen, estrogen, sperm count, vaginal secretion, Decreased ovary, uterus, vagina, breast size</td>
<td>Increased breast and endometrial cancer, cystocele, rectocele, atrophic vaginitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Increased NE, PTH, insulin, vasopressin</td>
<td>Increased DM, hypothyroidism, stress response</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Increased calcium loss from bone, Decreased muscle mass, cartilage</td>
<td>Increased arthritis, bursitis, osteoporosis, muscle weakness with gait abnormalities, polymyalgia rheumatica</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Atrophy of sebaceous and sweat glands, Decreased epidermal and dermal thickness, dermal vascularity, melanocytes, collagen synthesis</td>
<td>Increased lentigo, cherry hemangiomes, pruritus, seborheic keratosis, herpes zoster, decubitus ulcers, skin cancer</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>None</td>
<td>Increased depression, dementia, delirium, suicidality, substance abuse, anxiety, insomnia</td>
</tr>
</tbody>
</table>
Differential Diagnoses of Common Presentations

Constipation

- see Gastroenterology, G24

Definition
- less than 3 bowel movements in one week and/or hard stools, straining, sense of blockade, needing manual maneuvers or incomplete evacuation on more than 25% of occasions for at least 12 wk (does not need to be consecutive)

Epidemiology
- chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation)

Pathophysiology
- impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
- colorectal dysmotility

Treatment
- non-pharmacological
  - increase fiber intake
  - ensure adequate fluid intake
  - discourage chronic laxative use
  - engage in regular exercise
  - review medication regime, reduce dosages or substitute
- pharmacologic
  - see Common Medications, GM15

Risk Factors for Constipation in the Elderly Include:
- Immobility
- Diet: low fiber/calorie diet, dehydration
- Medications:
  - Polypharmacy
  - Drugs: narcotics, calcium channel blockers, anticholinergics
  - GI: obstructive lesions (bowel obstruction, cancer, diverticular disease, IBD, strictures, uterine prolapse), altered colonic motility (IBS, colonic inertia)
- Neurological: spinal cord injury, Parkinson’s disease, stroke, autonomic dysfunction
- Metabolic: diabetes, hypokalemia, hypercalcemia
- Psychiatric: depression, dementia

Figure 1. Treatment algorithm for the management of chronic constipation in the elderly
Adapted from: Clin Interv Aging 2010;5:163-171

Delirium, Dementia, and Depression

- see Psychiatry, PS16, PS17, PS7 and Neurology, N19

Definition
- pathologic decrease in memory, language, or executive function

Differential Diagnosis
- delirium, dementia, or pseudodementia of depression
Table 3. Differentiating the Three Ds of Cognitive Impairment

<table>
<thead>
<tr>
<th></th>
<th>Dementia</th>
<th>Delirium</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual or step-wise decline</td>
<td>Acute (hours-days)</td>
<td>Subacute</td>
</tr>
<tr>
<td>Duration</td>
<td>Months-years</td>
<td>Days-weeks</td>
<td>Variable</td>
</tr>
<tr>
<td>Natural History</td>
<td>Progressive, usually irreversible</td>
<td>Fluctuating, reversible</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Normal</td>
<td>Fluctuating</td>
<td>Normal</td>
</tr>
<tr>
<td>Attention</td>
<td>Intact initially</td>
<td>Decreased, wandering</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Orientation</td>
<td>Intact initially</td>
<td>Impaired, fluctuates</td>
<td>Intact</td>
</tr>
<tr>
<td>Behavior</td>
<td>Disinhibition, loss of ADL/ IADLs, personality change</td>
<td>Severe agitation/retardation</td>
<td>Importuning, self-harm/ suicide</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
<td>Slowing</td>
</tr>
<tr>
<td>Sleep-Wake Cycle</td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep-wake cycle</td>
<td>Early morning awakening</td>
</tr>
<tr>
<td>Mood and Affect</td>
<td>Labile but not usually anxious</td>
<td>Anxious, irritable, fluctuating</td>
<td>Depressed, stable</td>
</tr>
<tr>
<td>Cognition</td>
<td>Decreased executive function, paucity of thought</td>
<td>Fluctuation preceded by mood changes</td>
<td>Concentration impaired</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
<td>Recent</td>
</tr>
<tr>
<td>Language</td>
<td>Agnosia, aphasia, decreased comprehension, repetition</td>
<td>Dysnomia, dysgraphia, speech rambling, subject changes, incoherence</td>
<td>Not affected</td>
</tr>
<tr>
<td>Delusions</td>
<td>Compensatory</td>
<td>Nightmarish, poorly formed</td>
<td>Nihilistic, somatic</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Variable, vacuous, bland</td>
<td>Visual common, frightening/bizarre</td>
<td>Self-deprecatory</td>
</tr>
</tbody>
</table>

Delirium Prevention in Elderly
- ensure optimal vision and hearing to support orientation (e.g. appropriate eyewear and hearing aids)
- provide adequate nutrition and hydration (up in chair to eat and drink whenever feasible)
- encourage regular mobilization to build and maintain strength, balance, and endurance
- avoid unnecessary medications and monitor for drug interactions
- avoid bladder catheterization if possible
- ensure adequate sleep

Elder Abuse

Definition
- includes physical abuse, sexual abuse, emotional/psychological abuse, financial abuse, abandonment, and neglect
- in the U.S., most states have criminal penalties for elder abuse

Epidemiology
- in the U.S., estimates of the frequency of elder abuse range from 3-8%
- insufficient evidence to include/exclude screening in the Periodic Health Exam

Risk Factors

Table 4. Risk Factors for Elder Abuse

<table>
<thead>
<tr>
<th>Situational Factors</th>
<th>Victim Characteristics</th>
<th>Perpetrator Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation</td>
<td>Physical or emotional dependence on caregiver</td>
<td>Related to victim</td>
</tr>
<tr>
<td>Unstable or unsafe living arrangements</td>
<td>Lack of family ties</td>
<td>Living with victim</td>
</tr>
<tr>
<td>Lack of family, community or living facility resources for additional care</td>
<td>History of family violence</td>
<td>Long duration of care for victim (mean 9.5 yr)</td>
</tr>
<tr>
<td></td>
<td>Dementia or recent deterioration in health</td>
<td>Financial, marital, occupational or other stressors</td>
</tr>
</tbody>
</table>

Caregiver Abuse Screen (CASE)
• instructions
  ▪ to be answered by caregivers, if answer “yes” to a question, further explore issue
  ▪ the more “yes” responses, the more likely the presence of abuse
• screening tool
  ▪ please answer the following questions as a helper/caregiver
    1. Do you sometimes have trouble making ______ control his/her temper or aggression?
    2. Do you often feel you are being forced to act out of character/do things you feel badly about?
    3. Do you find it difficult to manage ______’s behavior?
    4. Do you sometimes feel that you are forced to rough with ______?
    5. Do you sometimes feel that you can’t do what is really necessary or what should be done for ______?
    6. Do you often feel you have to reject/ignore ______?
    7. Do you often feel so tired and exhausted that you cannot meet ______’s needs?
    8. Do you often feel you have to yell at ______?

From: NICE. Case: Caregiver Abuse Screen. 2010. Reproduced with permission from NICE

Management
• assess safety and determine capacity to make decisions about living arrangements
• establish need for hospitalization or alternate accommodation (e.g. immediate risk of physical harm by self or caregiver)
• involve multidisciplinary team (e.g. nurse, social worker, family members, and physicians including geriatrician, psychiatrist or family physician)
• educate and assist caregiver, contact local resources (e.g. legal aid, crisis support, PSW, caregiver support groups)
• interpret critical and lab findings that are key in exclusion, differentiation and diagnosis

Falls

Epidemiology
• 30-40% of people >65 yr old and ~50% of people >80 yr old fall each yr
  ▪ equally common between men and women, but more likely to result in injury in women
  ▪ 5% of falls lead to hospitalization
  ▪ falls are the leading cause of death in injury in persons older than 65 yr
  ▪ 25% associated with serious injuries (e.g. hip fracture, head injury, bruises, laceration)
  ▪ between 25-75% do not recover to previous level of ADL function
  ▪ mortality increases with age (171/100,000 in men >85 yr old) and type of injury (25% with hip fracture die within 6 mo)

Etiology
• multifactorial
  • extrinsic
    ▪ environmental (e.g. home layout, lighting, stairs, footwear), accidental, abuse
    ▪ medications/substances (e.g. alcohol)
    ▪ acute illness, exacerbation of chronic illness
  • intrinsic
    ▪ orthostatic/syncopal
    ▪ age-related changes and diseases associated with aging: musculoskeletal (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), metabolic (glucose, electrolytes)

Investigations
• directed by history and physical
• comprehensive geriatric assessment to identify all potential causes
• CBC, electrolytes, BUN, creatinine, glucose, Ca²⁺, TSH, B₁₂, urinalysis, cardiac enzymes, ECG, CT head

Prevention
• multidisciplinary, multifactorial, health, and environment risk factor screening and intervention programs in the community
• muscle strengthening, balance retraining, and group exercise programs (e.g. tai chi)
• home hazard assessment and modification (e.g. remove rugs, add shower bars, etc.)
• prescription of vitamin D 1000 IU daily
• tapering or gradually discontinuation of psychotropic medication
• postural hypotension, heart rate, and rhythm abnormalities management
• eyesight and footwear optimization

Red Flags for Elder Abuse
• Delay in seeking medical attention
• Disparity in histories
• Implausible or vague explanations
• Frequent emergency room visits for exacerbations of chronic disease despite plan for medical care and adequate resources
• Presentation of functionality impaired patient without designated caregiver
• Lab findings inconsistent with history

Key Physical Findings in the Elderly Patient Who Falls or Nearly Falls

I HATE FALLING
Inflammation of joints
Hypotension (orthostatic changes)
Auditory and visual abnormalities
Tremor
Equilibrium (balance) problem
Foot Problems
Arrhythmia, heart block or valvular disease
Leg-length discrepancy
Lack of conditioning (generalized weakness)
Illness
Nutrition
Gait disturbance

A history of falls within the past 1-2 yr is a predictor of motor vehicle crashes in the older population. These patients should be evaluated on their ability to drive and counseled about driving.

Drugs That May Increase the Risk of Falling
• Sedative-hypnotic and anxiolytic drugs (especially long-acting benzodiazepines)
• Antidepressants (including MAOIs, SSRIs, TCAs)
• Antipsychotics and tranquilizers (phenothiazines and butyrophenones)
• Antihypertensive drugs
• Antiarrhythmics (Class IA)
• Diuretics
• Systemic corticosteroids
• NSAIDs
• Anticholinergic drugs
• Hypoglycemic agents
• Alcohol

Adapted from: Am Fam Physician 2001;61:2159-2172
Table 5. Common Medical Conditions Associated with Failure to Thrive

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Cause of Failure to Thrive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Metastases, malnutrition, cachexia</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>Steroid myopathy, diabetes, osteoporosis, vision loss</td>
</tr>
<tr>
<td>Cirrhosis, hepatitis</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Depression, other psychiatric disorder</td>
<td>Major depression, psychosis, poor functional status, cognitive loss</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Malabsorption, poor glucose homeostasis, end-organ damage</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Hip, long bone fracture</td>
<td>Functional impairment</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Myocardial infarction, congestive heart failure</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Recurrent UTI, pneumonia</td>
<td>Chronic infection, functional impairment</td>
</tr>
<tr>
<td>Rheumatologic disease (GCA, RA, SLE)</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Stroke</td>
<td>Dysphagia, depression, cognitive loss, functional impairment</td>
</tr>
<tr>
<td>Tuberculosis, other systemic infection</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>

Adapted from: Clin Genet Med 1997;13:769-778

Frailty (Failure to Thrive)

Definition
- declining independence and functional capacity with loss of energy, vigor, and/or weight in older adults
- not an inevitable consequence of aging

Etiology
- malnutrition, functional impairment, cognitive impairment, and depression
Incontinence

**Fecal Incontinence**

**Epidemiology**
- Second leading cause of nursing home placement

**Etiology**
- Commonly multifactorial
  - Structural abnormalities
  - Trauma (e.g., prior vaginal delivery, surgery)
  - Prolapse
  - Tumor/trauma (e.g., brain, spinal cord, cauda equina)
- Functional abnormalities
  - Neurologic conditions – neuropathy, multiple sclerosis, stroke, dementia
- Others
  - Constipation with overflow may be a factor
  - Psychosis (willful soiling)
  - Age >80 yr: decreased external sphincter strength and weak anal squeeze, increased rectal compliance, decreased resting tone and internal sphincter, impaired anal sensation
- Medications (e.g., laxatives, anticholinergics, antidepressants, caffeine, muscle relaxants)

**Investigations (if cause not apparent from history and physical)**
- Differentiate true incontinence from frequency and urgency (i.e., IBS, IBD)
- Stool studies
- Anal or rectal ultrasound
- Colonoscopy, sigmoidoscopy, anoscopy
- Anorectal manometry or functional testing

**Management**
- Diet/bulking agent if stool is liquid or loose
- Disimpaction, prevent impaction
- Anti-diarrheal agents (e.g., loperamide)
- Regular defecation program in patients with dementia
- Counsel about biofeedback therapy (retraining of pelvic floor muscles)
URINARY INCONTINENCE

- see Urology, U5

Epidemiology

- 15-30% prevalence dwelling in community and at least 50% of institutionalized seniors
- morbidity: cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality

Pathophysiology

- not a normal part of aging, urinary incontinence is a loss of control due to a combination of:
  - genitourinary pathology: increased post-void residual volume, increased involuntary bladder contractions (urge incontinence)
  - age-related changes: decreased bladder capacity
  - comorbid conditions and medications
  - functional impairment
- in elderly women: decline in bladder outlet and urethral resistance pressure promoting stress incontinence
- in elderly men: prostatic enlargement can cause overflow and urge incontinence

Gait Disorders

- see Neurology, N34

Hazards of Hospitalization

Table 6. Recommendations for Sequelae of Hospitalization in Older Patients

<table>
<thead>
<tr>
<th>Sequelae</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>No dietary restrictions (except diabetes), assistance, dentures if necessary, sitting in a chair to eat</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Medication review, remove environmental barriers, discontinue use of catheter</td>
</tr>
<tr>
<td>Depression</td>
<td>Routine screening</td>
</tr>
<tr>
<td>Adverse drug event</td>
<td>Medication review</td>
</tr>
<tr>
<td>Confusion/delirium</td>
<td>Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints</td>
</tr>
<tr>
<td>Pressure ulcers</td>
<td>Low-resistance mattress, daily inspection, repositioning every 2 h</td>
</tr>
<tr>
<td>Infection</td>
<td>Early mobilization, remove unnecessary IV lines, catheters, NG tubes</td>
</tr>
<tr>
<td>Falls</td>
<td>Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review</td>
</tr>
<tr>
<td>Hypotension/dehydration</td>
<td>Early recognition and repletion</td>
</tr>
<tr>
<td>Diminished aerobic capacity/loss of muscle strength/contractures</td>
<td>Early mobilization</td>
</tr>
<tr>
<td>Decreased respiratory function</td>
<td>Incentive spirometry, physiotherapy</td>
</tr>
</tbody>
</table>

Hypertension

- see Family Medicine, FM35
- 60-80% of elderly (>65 yr old) have HTN
  - 60% of these have isolated systolic HTN
  - the benefit of treating HTN in the elderly is 2-4 times greater than that achieved in the treatment of younger patients with primary HTN
  - systolic and pulse pressure are major predictors of outcome in the elderly patient
  - in older adults, base treatment on sBP
  - target BP: sBP <140, dBP <90; for patients with DM: sBP <130, dBP <80
  - more recently, some argue a target of sBP <140 reasonable for all elderly patients, and minimizes risk of hypertension
- treatment:
  - non-pharmacologic treatments are first-line, then thiazide monotherapy is recommended
  - add ACEI/ARB if also atherosclerosis, DM, CHF or chronic kidney disease
  - add β-blockers if also angina or CHF
**Immobility**

**Complications**
- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- musculoskeletal: atrophy, contractures, bone loss
- skin: pressure ulcers
- psychological: sensory deprivation, delirium, depression

**Immunizations**

- the following immunizations are recommended for people 65 yr of age and older
  - tetanus: every 10 yr
  - pneumococcus: every 5 yr
  - influenza: every autumn
  - herpes zoster: Zostivax

**Malnutrition**

**Definition**
- involuntary weight loss of ≥5% baseline body weight or ≥5 kg
- hypoalbuminemia, hypocholesterolemia

**Etiology**
- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals or feeding oneself due to functional impairment)
- stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical: dental problems, dysphagia
- age-related changes: appetite dysregulation, decreased thirst
- mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

**Clinical Features**
- history
  - recent or chronic illness
  - depression, GI symptoms
  - functional disability: impaired ADLs and IADLs
  - social factors: economic barriers, dental problems and living situation (e.g. living alone)
  - constitutional symptoms (e.g. recent weight loss)
- physical exam
  - BMI <23.5 in males, <22 in females should raise concern
  - temporal wasting, muscle wasting, presence of triceps skin fold
  - assess cognition

**Investigations**
- CBC, electrolytes, Ca²⁺, Mg²⁺, PO₄³⁻, creatinine, LFTs (albumin, INR, bilirubin), B₁₂, folate, TSH, transferrin, lipid profile, urinalysis, ESR, CXR

**Osteoporosis**

- see Endocrinology E42

**Presbycusis**

- see Otolaryngology OT20
Pressure Ulcers

- see Plastic Surgery, PL16

Risk Factors
- extrinsic factors: friction, pressure, shear force
- intrinsic factors: immobility, malnutrition, moisture, sensory loss

Table 7. Classification of Pressure Ulcers

| Stage I | Changes include skin temperature, tissue consistency or sensation
| An area of persistent erythema in lightly pigmented, intact skin; in darker skin, it may appear red, blue or purple |
| Stage II | Partial thickness skin loss involving the epidermis, dermis or both
| The ulcer is superficial and presents as an abrasion, blister or shallow crater |
| Stage III | Full thickness skin loss involving damage or necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia
| Presents as a deep crater with or without undermining of adjacent tissue |
| Stage IV | Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures
| May have associated undermining and/or sinus tracts |

Prevention
- pressure reduction
  - frequent repositioning
  - pressure-reducing devices (static, dynamic)
- maintaining nutrition, encouraging mobility and managing incontinence

Treatment
- optimize nutritional status
- minimize pressure on wound
- analgesia
- wound debridement (mechanical, enzymatic, autolytic) and dressing application
- maintain moist wound environment to enable re-epithelialization
- treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
- swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
- stage IV ulcers typically warrant surgical debridement
- consider other treatment options
  - negative pressure wound therapy/vacuum-assisted closure (VAC)
  - biological agents: application of fibroblast growth factor, platelet-derived growth factor to wound
  - non-contact normothermic wound therapy
  - electrotherapy

Driving Competency

Reporting Requirements
- not an issue unique to geriatrics – any patient may suffer from a medical condition that impairs their ability to drive should be reported
- in the U.S., varies by state

Conditions that may Impair Driving

Table 8. Conditions that Impair Driving

| Alcohol | Patients with history of impaired driving and those with high probability of future impaired driving should not drive until further assessed
| Alcohol dependence or abuse: if suspected, should be advised not to drive
| Alcohol withdrawal seizure: must complete a rehabilitation program and remain abstinent and seizure-free for 6 mo before driving |
| Blood Pressure | HTN: sustained BP > 170/110 should be evaluated carefully
| Hypotension: if syncopeal, discontinue until attacks are treated and preventable |
### Table 8. Conditions that Impair Driving (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Disease</td>
<td>Suspected asymptomatic CAD or stable angina: no restrictions</td>
</tr>
<tr>
<td></td>
<td>STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for one month following hospital discharge</td>
</tr>
<tr>
<td></td>
<td>NSTEMI with mild LV damage, unstable angina: no driving for 48 h if percutaneous coronary intervention (PCI) performed or 7 d if no PCI performed</td>
</tr>
<tr>
<td>Cerebrovascular Conditions</td>
<td>TIA: should not be allowed to drive until a medical assessment is completed</td>
</tr>
<tr>
<td></td>
<td>Stroke: should not drive for at least one month; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure</td>
</tr>
<tr>
<td>COPD</td>
<td>Mild/moderate impairment; no restrictions</td>
</tr>
<tr>
<td></td>
<td>Moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen</td>
</tr>
<tr>
<td>Cognitive Impairment/Dementia</td>
<td>Moderate to severe dementia is a contraindication to driving; defined as the “inability to independently perform 2 or more IADLS or any basic ADL”</td>
</tr>
<tr>
<td></td>
<td>Patients with mild dementia should be assessed; if indicated, refer to specialized driving testing center; if deemed fit to drive, re-evaluate patient every 6-12 mo</td>
</tr>
<tr>
<td></td>
<td>Poor performance on MMSE, clock drawing or Trails B suggests a need to investigate driving ability further</td>
</tr>
<tr>
<td></td>
<td>MMSE score alone (whether normal or low) is insufficient to determine fitness to drive</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular or cerebrovascular disease)</td>
</tr>
<tr>
<td></td>
<td>Insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 mo</td>
</tr>
<tr>
<td>Drugs</td>
<td>Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants</td>
</tr>
<tr>
<td></td>
<td>Degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving until condition resolves</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>Effect of impaired hearing on ability to drive safely is controversial</td>
</tr>
<tr>
<td></td>
<td>Acute labyrinths, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td>Physician’s role is to report etiology, prognosis and extent of disability (pain, range of motion, coordination, muscle strength)</td>
</tr>
<tr>
<td>Post-Operative</td>
<td>Outpatient, conscious sedation: no driving for 24 h</td>
</tr>
<tr>
<td></td>
<td>Outpatient, general anesthesia: no driving for ≥24 h</td>
</tr>
<tr>
<td>Seizures</td>
<td>First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head Epilepsy: can drive if seizure-free on medication and physician has insight into patient compliance</td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>Visual acuity: contraindicated to drive if &lt;20/50 with both eyes examined simultaneously</td>
</tr>
<tr>
<td></td>
<td>Visual field: contraindicated to drive if &lt;120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously</td>
</tr>
</tbody>
</table>

N.B. guidelines included refer specifically to private driving.

### Health Care Institutions

#### Table 9. Classification of Health Care Services and Institutions

<table>
<thead>
<tr>
<th>Institution/Service</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home Health Agency</td>
<td>Health care services offered at home for those who can live independently at home or under the care of family members including professional health care services, personal care and support (ADL), homemaking, support services such as transportation, meal delivery, day programs, caregiver relief, security checks, etc.</td>
</tr>
<tr>
<td>Residential</td>
<td>Divided into short (&lt;60-90 d/yr) and long (indefinite) stay</td>
</tr>
<tr>
<td>a) Seniors Affordable Housing</td>
<td>Seniors who live independently and manage their own care but prefer to live near other seniors; usually has accessibility features and rent is adjusted based on income</td>
</tr>
<tr>
<td>b) Retirement/Nursing Home</td>
<td>Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned</td>
</tr>
<tr>
<td>c) Supportive Housing</td>
<td>Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment and may offer some physiotherapy and rehabilitation services</td>
</tr>
<tr>
<td>d) Long-term Care/Skilled Nursing Facility</td>
<td>Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy, and rehabilitation services; may be used short-term for caregiver respite, or for supportive patient care to regain strength and confidence after leaving the hospital</td>
</tr>
<tr>
<td>e) Hospice</td>
<td>Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤3 mo</td>
</tr>
</tbody>
</table>
names of community health care institutions, types of facilities, and services offered vary between geographical locations
factors to consider when seeking services/institutions include level of care required, support networks, duration of stay, and cost

Palliative and End-of-Life Care

Principles and Quality of Life

- support, educate, and treat both patient and family
- address physical, psychological, social and spiritual needs
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

End-of-Life Care Discussions

When to Initiate End-of-Life Care Discussions
- recent hospitalization for serious illness
- severe progressive medical condition(s)
- death expected within 6-12 mo
- patient inquires about end-of-life care

Suggested Topics for Discussion
- goals of care (disease vs. symptom management)
- advance directives, power of attorney, public guardian and trustee
- treatment options and likelihood of success
- common medical interventions
  - mechanical ventilation
  - antibiotic therapy
  - feeding tubes
- resuscitation options and likelihood of success (Full Code vs. DNR status including preferences for CPR, intubation, ICU admission, artificial hydration)

Power of Attorney

- see Ethical, Legal, and Organizational Medicine, ELOAM8

Instructional Advance Directives

- see Ethical, Legal, and Organizational Medicine, ELOAM8

Symptom Management

Assessment Tools
- Edmonton Symptom Assessment System (ESAS): a tool that asks patients to rate the intensity of symptoms from 0-10 and allows for tracking of the efficacy of interventions. Assesses: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well being, shortness of breath, and “other problem”
- Palliative Performance Scale (PPS): a tool that uses functional status to predict survival in terminally ill patients. Assesses 5 components: ambulation, activity and evidence of disease, self-care, intake and conscious level

Source: J Pain Palliat Care 1991;7:6-9 and Victoria Hospice Society 2006;120-121
**Geriatric Pharmacology**

### Pharmacokinetics

#### Table 11. Age-Associated Pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age Effect</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (less</td>
<td>Increased gastric pH, decreased splanchic blood flow, GI absorptive surface</td>
<td>Drug-drug and drug-food interactions are more likely</td>
</tr>
<tr>
<td>significant)</td>
<td>and dermal vascularity; delayed gastric emptying</td>
<td>to affect absorption</td>
</tr>
<tr>
<td>Distribution</td>
<td>Increased total body fat and α1-glycoprotein</td>
<td>Lipophilic drugs have a larger volume of distribution</td>
</tr>
<tr>
<td>Metabolism (less</td>
<td>Decreased lean body mass, total body water and albumin</td>
<td>Decreased binding of acidic drugs, increased binding</td>
</tr>
<tr>
<td>significant)</td>
<td>Impaired phase I reactions (oxidative system)</td>
<td>of basic drugs</td>
</tr>
<tr>
<td>Elimination</td>
<td>Decreased renal blood flow, GFR, tubular secretion and renal mass</td>
<td>For every % reduction in clearance, decrease the dose</td>
</tr>
</tbody>
</table>


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**WHO’s Pain Relief Ladder**

- **Opioid for moderate to severe pain ± Non-opioid ± Adjuvant**
- **Pain persisting or increasing**

**Opioid Equivalent Doses (to 10 mg of IV morphine)**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>SC/IV dose</th>
<th>PO dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>20-30 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>Not recommended</td>
<td>180-240 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Not recommended</td>
<td>10-15 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
<td>4-6 mg</td>
</tr>
<tr>
<td>Fentanyl transdermal</td>
<td>25 µg/h = morphine 90 mg</td>
<td>PO/24 h, however fentanyl takes 12-16 h to reach steady state</td>
</tr>
</tbody>
</table>

---

**Death Rattle**

Noise caused by the oscillatory movement of mucous secretions in the upper airway with inspiration and expiration

**Nociceptive Pain**

Somatic: localized to bone/skin/joint/muscle; gnawing, dull pain
Visceral: not well localized; crampy pain, pressure

**Neuropathic Pain**

Burning, shooting, radiating pain; localized to dermatomal regions

---

Serum creatinine does not reflect creatinine clearance in the elderly, as they can have falsely lowered serum creatinine levels. Some advocate for rounding geriatrics’ patients low serum creatinine numbers to 1 mg/dL, however this is controversial.
Pharmacodynamics

Drug Sensitivity
• changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
• increased sensitivity to warfarin, sedatives, antipsychotics, digoxin and narcotics
• decreased sensitivity to β-blockers in majority of elderly patients, though some may have increased sensitivity

Decreased Homeostasis
• poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

Polypharmacy

Definition
• prescription, administration or use of five or more medications at the same time

Epidemiology
• patients over 65 years old are the largest medication consumers in the United States
• many elderly patients do not understand their medications
• hospitalized elderly are given an average of 10 medications during admission

Risk Factors for Non-Compliance
• risk of non-compliance correlates with medication factors, not age
  ▪ number of medications – compliance with 1 medication is 80%, but drops to 25% with ≥6 medications
• increased dosing frequency, complicated container design, financial constraints, and cognitive impairment

Adverse Drug Reactions
• any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
• risk factors in the elderly
  ▪ intrinsic: comorbidities, age-related changes in pharmacokinetics and pharmacodynamics
  ▪ extrinsic: number of medications, multiple prescribers, unreliable drug history
• 90% of ADRs are from: ASA, analgesics, anticoagulants, antimicrobials, antineoplastics, digoxin, diuretics, hypoglycemics, steroids

Preventing Polypharmacy
• consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
• consider patient: other medications, clinical indications, medical comorbidities
• consider patient-drug interaction risk factors for ADRs
• review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
• avoid treating an ADR with another medication

Inappropriate Prescribing in the Elderly

Epidemiology
• the estimated prevalence of potentially inappropriate prescribing ranges from 12-40%

Beers Criteria
• a list of medications to avoid in adults 65 and older due to safety concerns
• examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives
• the elderly are also often under-treated (ACEI, ASA, β-blockers, thrombolytics, warfarin)

Beers Criteria of Choice in the Elderly
LOT
Lorazepam
Oxazepam
Temazepam

Approach to Medication Review in the Elderly
NO TEARS
Need and indication
Open-ended questions (to get patient’s perspective on medications)
Tests and monitoring (to assess disease control)
Evidence and guidelines
Adverse events
Risk reduction (of adverse events such as falls)
Simplification/switches

New medications: Start Low, Go Slow!

Principles for Prescribing in the Elderly
CARED
Caution/Compliance
Age (adjust dosage for age)
Review regimen regularly
Educate
Discontinue unnecessary medications

Adverse drug reactions in the elderly may present as delirium, falls, fractures, urinary incontinence/retention or fecal incontinence/impaction

Beers Criteria
For full list of medications, consult the following reference:
The American Geriatrics Society 2012 Beers Criteria Update Expert Panel
J Am Geriatr Soc 2012;60(4):616-31
http://www.americangeriatrics.org
## Table 12. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANALGESICS (non-opioid)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>acetaminophen</td>
<td>Tylenol®</td>
<td>325-650 mg PO q4-6h prn (up to 4 g/d)</td>
<td>Fever, mild pain</td>
<td>Lower doses for hepatic and renal disease, chronic alcoholism, known hypersensitivity</td>
<td>Hepatotoxicity (in overdose)</td>
<td>Prostaglandin-synthesis inhibition, no anti-inflammatory effects</td>
</tr>
<tr>
<td>ibuprofen</td>
<td>Advil®</td>
<td>200-800 mg PO q4-6h prn (up to 1200 mg/d)</td>
<td>Mild to moderate pain, inflammatory disorders, fever</td>
<td>Active GI bleed/ulcer disease, known hypersensitivity, severe renal or hepatic disease</td>
<td>Dyspepsia, nausea, diarrhea, dizziness, rash, GI toxicity (ulcer, perforation, bleed)</td>
<td>Prostaglandin-synthesis inhibition, anti-inflammatory effects</td>
</tr>
<tr>
<td>celecoxib</td>
<td>Celebrex®</td>
<td>200 mg PO daily or 100 mg PO bid</td>
<td>Osteoarthritis, rheumatoid arthritis, FAP</td>
<td>Cardiovascular or cerebrovascular disease, CABG (perioperative), sulfonamide or ASA/NSAID allergy, active GI bleed/ulcer, IBD, severe renal or hepatic disease, hyperkalemia</td>
<td>GI symptoms (pain, diarrhea, dyspepsia, flatus), GI bleed, serious cardiovascular events</td>
<td>COX-2 inhibitor, analgesic, anti-inflammatory and anti-pyretic effects</td>
</tr>
<tr>
<td><strong>ANALGESICS (opioid)</strong></td>
<td></td>
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<tr>
<td></td>
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</tr>
<tr>
<td><strong>ANTI-HYPERTENSIVES</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>thiazide diuretic e.g. hydrochlorothiazide</td>
<td>Hydrodiuril®</td>
<td>12.5-25 mg PO daily</td>
<td>HTN, edema</td>
<td>Anuria, hepatic coma, precoma, known sensitivity to thiazides</td>
<td>Hypotension, transient hyperlipidemia, hypokalemia and other electrolyte disturbances, hyperuricemia, GI symptoms</td>
<td>Inhibition of Na⁺/Cl⁻ co-transporter</td>
</tr>
<tr>
<td>ACEI e.g. ramipril</td>
<td>Altace®</td>
<td>2.5-20 mg PO daily</td>
<td>Essential HTN, post-MI, cardiovascular disease, renal protection</td>
<td>Known hypersensitivity, angioedema</td>
<td>Hypotension, cough, headache, dizziness, asthma, chest pain, nausea, peripheral edema, arthritis, dyspnea, angioedema, hyperkalemia</td>
<td>Inhibition of angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ARB e.g. losartan</td>
<td>Cozaar®</td>
<td>50-100 mg PO daily</td>
<td>Essential HTN (± diabetes mellitus)</td>
<td>Known hypersensitivity</td>
<td>Dizziness, hypotension, fatigue, headache, hyperkalemia</td>
<td>Antagonizes angiotensin II via blockade of the angiotensin type 1 receptor</td>
</tr>
<tr>
<td>DHP CCB e.g. amlodipine</td>
<td>Norvasc®</td>
<td>2.5-10 mg PO daily (initially)</td>
<td>Essential HTN, chronic stable angina</td>
<td>Known hypersensitivity, severe hypotension, caution in aortic stenosis</td>
<td>Edema, muscle cramps, dizziness, headache, constipation, heartburn</td>
<td>Calcium ion influx inhibition</td>
</tr>
<tr>
<td><strong>COGNITIVE ENHANCERS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>donepezil</td>
<td>Aricept®</td>
<td>5-10 mg PO daily</td>
<td>Moderate to severe dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, caution in pulmonary disease, sick sinus syndrome, seizure disorder</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion</td>
<td>Reversible inhibition of acetylcholinesterase</td>
</tr>
<tr>
<td>galantamine</td>
<td>Razadyne®</td>
<td>8-12 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, caution in sick sinus syndrome, seizure disorder, pulmonary disease, low body weight</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion</td>
<td>Reversible inhibition of acetylcholinesterase</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>Exelon®</td>
<td>1.5 mg PO daily (starting) up to 6 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, severe hepatic disease, caution in sick sinus syndrome, pulmonary disease, seizure disorder</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion</td>
<td>Acetylcholinesterase inhibition (reversible but very slow)</td>
</tr>
<tr>
<td>memantine</td>
<td>Ebixa®/Namenda® (Can)/(U.S.)</td>
<td>5 mg PO daily (starting) up to 10 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, conditions that alkalize urine, caution in cardiovascular conditions</td>
<td>Agitation, fatigue, dizziness, headache, HTN, constipation</td>
<td>NMDA-receptor antagonist</td>
</tr>
</tbody>
</table>
**Table 12. Common Medications (continued)**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAXATIVES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bran</td>
<td>All-Bran®</td>
<td>1 cup/d</td>
<td>Constipation</td>
<td></td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
</tr>
<tr>
<td>psyllium</td>
<td>Metamucil®</td>
<td>1 tsp PO tid</td>
<td>Constipation, hypercholesterolemia</td>
<td>N/V, abdominal pain, obstruction</td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
</tr>
<tr>
<td>lactulose</td>
<td>Chronulac®, Cephulac®, Kristalose®</td>
<td>15-30 cc PO daily/bid</td>
<td>Constipation, hepatic encephalopathy, bowel evacuation following barium exam</td>
<td>Patients on low galactose diets</td>
<td>Flatus, cramps, nausea, diarrhea</td>
<td>Hyperosmolar agent, lowers pH of colon to decrease blood ammonia levels</td>
</tr>
<tr>
<td>senna</td>
<td>Senokot®, Ex-lax®, Glysenind®</td>
<td>1-2 tabs PO daily or 10-15 cc syrup PO daily</td>
<td>Constipation</td>
<td>Abdominal pain, N/V</td>
<td>Cramps, gripping, dependence</td>
<td>Stimulant laxative</td>
</tr>
<tr>
<td>bisacodyl</td>
<td>Dulcolax®</td>
<td>5-15 mg PO (10 mg PR)</td>
<td>Constipation</td>
<td>Ileus, obstruction, abdominal pain, N/V, severe dehydration</td>
<td>Cramps, pain, diarrhea</td>
<td>Stimulant laxative</td>
</tr>
</tbody>
</table>

**PARKINSONIAN AGENTS – see Neurology, N54**

**SLEEPING MEDICATIONS**

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>eszopiclone</td>
<td>Lunesta®</td>
<td>3.75 mg PO qhs (initially)</td>
<td>Insomnia</td>
<td>Known hypersensitivity, caution in myasthenia gravis, severe hepatic disease</td>
<td>Bitter taste, palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor, sweating</td>
<td>Short-acting hypnotic (no tolerance effects)</td>
</tr>
<tr>
<td>temazepam</td>
<td>Restoril®</td>
<td>15 mg PO qhs</td>
<td>Short-term management of insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, sleep apnea</td>
<td>Drowsiness, dizziness, impaired coordination, hangover, lethargy, dependence</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
<tr>
<td>lorazepam</td>
<td>Ativan®</td>
<td>0.5 mg PO qhs (initially)</td>
<td>Anxiety, insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, narrow-angle glaucoma</td>
<td>Dizziness, drowsiness, lethargy, dependence</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
</tbody>
</table>

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in the elderly.

---

**Landmark Geriatric Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study</td>
<td>Brain 2012; 135(9): 2009-16</td>
<td>First population study to show that delirium is a strong risk factor for dementia and cognitive decline in elderly patients</td>
</tr>
<tr>
<td>Donepezil and Memantine for Moderate-to-Severe Alzheimer’s Disease</td>
<td>NEJM 2012; 366:893-903</td>
<td>Continued treatment with donepezil was associated with cognitive benefits over the course of 12 mo in patients with moderate or severe Alzheimer’s disease</td>
</tr>
<tr>
<td>Early palliative care for metastatic lung cancer</td>
<td>NEJM 2010; 363:733-742</td>
<td>Among patients with metastatic non-small-cell lung cancer, early palliative care led to significant improvements in both quality of life and mood. As compared with patients receiving standard care, patients receiving early palliative care had less aggressive care at the end-of-life but longer survival</td>
</tr>
<tr>
<td>Hip protectors for fracture prevention</td>
<td>NEJM 2000; 343:1506-1513</td>
<td>The risk of hip fracture can be reduced in frail elderly adults by the use of an anatomically designed external hip protector</td>
</tr>
<tr>
<td>HYVET</td>
<td>NEJM 2008; 358:1887-1898</td>
<td>Antihypertensive treatment with indapamide (sustained release), with or without perindopril, in adults 90 yr or older is beneficial</td>
</tr>
<tr>
<td>PROFET</td>
<td>Lancet 1999; 353:93-97</td>
<td>Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment</td>
</tr>
<tr>
<td>Yale Delirium Prevention Trial</td>
<td>NEJM 1999; 340:659-676</td>
<td>A risk-factor intervention strategy can result in significant reductions in the number and duration of episodes of delirium in hospitalized older patients</td>
</tr>
</tbody>
</table>
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Health Status

Physiology and Pathology of Aging

Constipation

Delirium, Dementia, and Depression

Elder Abuse

Falls

Frailty

Hazards of Hospitalization

Hypertension

Immunizations

Malnutrition

Pressure Ulcers

Driving Competency
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Health Care Institutions
Palliative and End-of-Life Care


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**Acronyms**

- β-HCG: beta-human chorionic gonadotropin
- AFP: alpha-fetoprotein
- AIS: androgen insensitivity syndrome
- ASCUS: atypical squamous cells of undetermined significance
- AUB: abnormal uterine bleeding
- BMI: body mass index
- BSO: bilateral salpingo-oophorectomy
- BV: bacterial vaginosis
- CMV: cytomegalovirus
- DCS: dilatation and curettage
- DES: diethylstilbestrol
- DHEA: dihydroepiandrosterone
- DMPA: depo-medroxyprogesterone acetate or Depo-Provera®
- DUB: dysfunctional uterine bleeding
- DVT: deep venous thrombosis
- EPC: emergency postcoital contraception
- FSH: follicle-stimulating hormone
- GA: gestational age
- GIFT: gamete intrafallopian transfer
- GNRH: gonadotropin-releasing hormone
- GTN: gestational trophoblastic neoplasia
- GTD: gestational trophoblastic disease
- HERS: heart and estrogen/progestin replacement study
- HMG: human menopausal gonadotropin
- HPO: hypothalamic-pituitary-ovarian
- HRT: hormone replacement therapy
- HSV: herpes simplex virus
- ICSI: intracytoplasmic sperm injection
- IBD: inflammatory bowel disease
- ICSI: intracytoplasmic sperm injection
- IUD: intrauterine device
- IUI: intrauterine insemination
- IVF: in vitro fertilization
- JRA: juvenile rheumatoid arthritis
- LDLH: lactate dehydrogenase
- LEEP: loop electrosurgical excision procedure
- LH: luteinizing hormone
- LHRH: luteinizing hormone releasing hormone
- LMP: last menstrual period
- LL: lymph node
- LNM: last normal menstrual period
- LSI: low-grade squamous intraepithelial lesion
- LSV: lymphovascular space involvement
- MRKH: Mayer-Rokitansky-Küster-Hauser
- NN: natural killer
- OCP: oral contraceptive pill
- OD: oral glucose tolerance test
- PG: progestin
- PID: pelvic inflammatory disease
- PKD: polycystic kidney disease
- PMS: premenstrual syndrome
- PRP: rapid plasma reagin
- SCC: squamous cell carcinoma
- SERMs: selective estrogen receptor modifiers
- SES: socioeconomic class
- SHBG: sex hormone binding globulin
- SII: somatostatin
- SSRI: selective serotonin reuptake inhibitors
- STD: sexually transmitted disease
- TAH: total abdominal hysterectomy
- TET: tubal embryo transfer
- TH: total hysterectomy
- TOT: tension-free obturator tape
- TSH: thyroid stimulating hormone
- TTV: tension-free vaginal tape
- T2: transformation zone
- VDRL: venereal disease research laboratory
- VTE: venous thromboembolism
- VWD: von Willebrand's disease
- W/D: withdrawal
- WHI: Women's Health Initiative
- ZIFT: zygote intrafallopian transfer

**Basic Anatomy Review**

**A. EXTERNAL GENITALIA (Figure 1)**
- Refers to collectively as the vulva
- Blood supply: internal pudendal artery
- Sensory innervation: pudendal nerve
- Lymphatic drainage: inguinal nodes

**B. VAGINA**
- Muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
- Lined by rugated, stratified-squamous epithelium
- Upper vagina separated by cervix into anterior, posterior, and lateral fornices
- Blood supply: vaginal branch of internal pudendal artery with anastomoses from uterine, inferior vesical, and middle rectal arteries

**C. UTERUS**
- Thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  - Uterine corpus
  - Blood supply: uterine artery (branch of internal iliac artery)
  - Cervix
  - Blood supply: cervical branch of uterine artery
- Supported by the pelvic diaphragm, the pelvic organs, and 4 paired sets of ligaments
- Round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals then terminate in the labia majora
- Function: aneversion
- Blood supply: Sampson's artery (branch of uterine artery running through round ligament)
- Uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
- Function: mechanical support for uterus and contain autonomic nerve fibers
- Cardinal ligaments: extend from lateral pelvic wall and insert into lateral cervix and vagina
- Function: mechanical support, prevent prolapse
- Broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics
- Infundibulopelvic ligament: continuous tissue that connects ovary to pelvic wall
- Contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
- Position of the uterus:
  - Antverted (majority)
  - Retroverted

**Figure 1. Vulva and perineum**

**Figure 2. External genital organs**
D. FALLOPIAN TUBES
- 8-14 cm muscular tubes extending laterally from the uterus to ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

E. OVARIES
- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

Menstruation

Stages of Puberty
- see Pediatrics, P31
- adrenarche: increase in secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding

Anteversion: forward-tilted uterus
Anteflexion: bending of uterus so the fundus is thrust forward
Retroversion: backward-tilted uterus
Retroflexion: bending of uterus so the fundus is thrust backward

Determination of uterine position by clinical exam:
- If cervix faces anteriorly (under the urethra and less easily accessible), i.e. toward vaginal orifice, more likely RETROVERTED UTERUS
- If cervix faces posteriorly (easily accessible), i.e. toward sacrum or rectum, more likely ANTEVERTED UTERUS
- If uterus palpable on bimanual exam, more likely ANTEVERTED UTERUS

“Water under the bridge”
The ureters run posterior to the uterine arteries

Stages of Puberty
“Boobs, Pubes, Grow, Flow”
Thelarche, Pubarche, Growth spurt, Menarche

Tanner Stage
Thelarche
I. None
II. Breast bud
III. Further enlargement of areola and breasts with no separation of contours
IV. 2nd mound of areola and papilla
V. Areola recessed to general contour of breast – adult

Pubarche
I. None
II. Downy hair along labia only
III. Darker/coarse hair extends over pubis
IV. Adult type covers smaller area, no thigh involvement
V. Adult hair in quantity and type; extends over thighs
### Characteristics
- Menarche: 10-15 yr
- Average: 12.2 yr
- Entire cycle: 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

### Estrogen
**ESTROGEN** is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle.

**Estrogen effects:**
- On the follicles in the ovaries: Reduces atresia
- On the endometrium: Proliferation of glandular and stromal tissue
- On all target tissues: Decreases E receptors

### Progesterone
**PROGESTERONE** is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle).

**Progesterone effects:**
- On the endometrium:
  - Cessation of mitoses (stops building endometrium up)
- *"Organization"* of glands (initiates secretions from glands)
- Inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues:
  - Decrease E receptors (the "anti-estrogen" effect)
  - Decrease P receptors

---

### Table: Events of the Normal Menstrual Cycle

<table>
<thead>
<tr>
<th>Phase</th>
<th>Early</th>
<th>Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FOLLICULAR/PROLIFERATIVE PHASE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiating Events</td>
<td>↓ E and ↓ P</td>
<td>↑ FSH acts on ovarian granulosa cells</td>
<td>Growing follicles continue to secrete E</td>
</tr>
<tr>
<td><strong>HPO Axis</strong></td>
<td>↑ GnRH pulse frequency</td>
<td>↑ FSH</td>
<td>↑ LH pulse frequency</td>
</tr>
<tr>
<td>Hormones</td>
<td>↑ E from follicles (ovary)</td>
<td>E from follicles, especially from dominant follicle</td>
<td></td>
</tr>
<tr>
<td>Feedback on HPO Axis</td>
<td>Negative feedback E → ↓ FSH, ↓ LH</td>
<td>Positive feedback: E and P → ↑ FSH, ↑ LH</td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>↑ FSH → follicular growth in 3-30 follicles</td>
<td>↑ follicular growth (by reducing atresia) → ↑ E</td>
<td></td>
</tr>
<tr>
<td>Endometrium</td>
<td>Menses from P withdrawal (from end of previous cycle)</td>
<td>E builds up endometrium</td>
<td></td>
</tr>
<tr>
<td>Cervical Mucus</td>
<td>Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>Early-Mid</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LUTEAL/SECRETORY PHASE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OVULATION</td>
<td>Sudden switch from negative to positive feedback (E and P now ↑ FSH &amp; LH)</td>
<td>Switch back to negative feedback</td>
</tr>
<tr>
<td></td>
<td>↑ LH pulse amplitude (LH surge)</td>
<td>↓ LH</td>
</tr>
<tr>
<td></td>
<td>E peaks → LH surge → ovulation</td>
<td>↑ P from corpus luteum</td>
</tr>
<tr>
<td></td>
<td>P from corpus luteum</td>
<td>↓ P secondary to degeneration of corpus luteum</td>
</tr>
<tr>
<td></td>
<td>P stabilizes endometrium</td>
<td>Withdrawal of P → menses</td>
</tr>
</tbody>
</table>

*E = estrogen; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; HPO = hypothalamic-pituitary-ovarian; LH = luteinizing hormone; P = progesterone*
Premenstrual Syndrome

- **synonyms:** "ovarian cycle syndrome," "menstrual molimina" (moodiness)

**Etiology**
- multifactorial: not completely understood; genetics likely play a role
- CNS-mediated neurotransmitter interactions with sex steroids (progesterone, estrogen, and testosterone)
- serotonergic dysregulation – currently most plausible theory

**Diagnostic Criteria for Premenstrual Syndrome**
- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness, abdominal bloating, headache, swelling of extremities
- symptoms relieved within 4 d of onset of menses
- symptoms present in the absence of any pharmacologic therapy, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or economic performance

**Treatment**
- goal: symptom relief
- psychological support
- diet/supplements
  - avoid sodium, simple sugars, caffeine, and alcohol
  - calcium (1,200-1,600 mg/d), magnesium (400-800 mg/d), vitamin E (400 IU/d), vitamin B₆
- medications
  - NSAIDs for discomfort, pain
  - spironolactone for fluid retention: used during luteal phase
  - SSRIs: used during luteal phase x 14 d or continuously
  - OCP: primarily beneficial for physical/somatic symptoms
  - danazol: an androgen that inhibits the pituitary-ovarian axis
  - GnRH agonists if PMS is severe and unresponsive to treatment (may use prior to considering definitive treatment with BSO)
- mind/body approaches
  - regular aerobic exercise
  - cognitive behavioral therapy
  - relaxation, light therapy biofeedback, and guided imagery
- herbal remedies (variable evidence)
  - evening primrose oil, black cohosh, St. John's wort, kava, ginkgo, agnus castus fruit extract
- BSO if symptoms severe

Premenstrual Dysphoric Disorder

**Definition**
- official diagnosis in the DSM-5
- described as a more severe form of PMS with specific diagnostic criteria
- treatment with SSRIs (first line), and Yaz® OCP (highly effective)
Differential Diagnoses of Common Presentations

Abnormal Uterine Bleeding

- see Disorders of Menstruation, GY11
- definition: change in frequency, duration, or amount of menstrual flow
- classified as
  - amenorrhea: absence of menstrual periods
  - hypomenorrhea: bleeding that is decreased in amount
  - oligomenorrhea: bleeding occurring at intervals >35 d
  - polymenorrhea: bleeding occurring at intervals <21 d
  - menorrhagia/hypermenorrhea: bleeding at regular intervals that is prolonged in duration (>7 d) or excessive in amount (>80 cc per menstrual cycle)
  - metrorrhagia: bleeding at irregular intervals, particularly between expected menstrual periods
  - menometrorrhagia: excessive bleeding at usual time of menstrual periods and at other irregular intervals
  - postmenopausal bleeding: any bleeding that presents >1 yr after menopause; must rule out endometrial cancer

Dysmenorrhea

- see Disorders of Menstruation, GY9
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechieae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease
  - IUD (copper)
  - foreign body

Vaginal Discharge/Pruritus

- see Gynecological Infections, GY23
- physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis
  - desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)
Pelvic Pain

Figure 6. Approach to pelvic pain

Pelvic Mass

Figure 7. Differential diagnosis of pelvic mass
Dyspareunia

Figure 8. Approach to dyspareunia

Common Investigations and Procedures

Imaging

Ultrasound
- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if β-hCG ≥1,500 (β-hCG must be ≥6,500 for transabdominal U/S)
- may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterize fibroids
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal women

Endometrial Biopsy
- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cytotec) if nulliparous or postmenopausal
- more invasive procedure (D&C) may be done in the office or operating room ± hysteroscopy
- indications
  - AUB/PMB
  - cancer screening (e.g. following specific cervical cytology results (i.e. AGUS) or in high-risk women)

Hysterectomy

Indications
- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications
- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)
Approaches
1. vaginal vs. abdominal
   • indications for vaginal approach: mobile uterus, uterine size <12 wk
   • advantages of vaginal approach: less pain, faster recovery time, allows for simultaneous repair of rectocele/cystocele/enterocele, improved aesthetics
2. open vs. laparoscopic-assisted
   • advantages of laparoscopy: less pain, faster recovery, improved aesthetics, shorter hospital stay
   • unless contraindicated or unavailable laparoscopic hysterectomy is the standard of care
3. robotic
   • similar advantages to laparoscopy
   • more dexterous

Table 1. Classification of Hysterectomy

<table>
<thead>
<tr>
<th>Classification Tissues Removed</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal Hysterectomy</td>
<td>Uterus</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Total Hysterectomy (extrafusal simple hysterectomy/type 1)</td>
<td>Uterus, cervix, uterine artery ligated at uterus</td>
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<tr>
<td>Total Hysterectomy (extrafusal simple hysterectomy/type 1) + Bilateral Salpingo-Oophorectomy</td>
<td>Uterus, cervix, uterine artery ligated at uterus, fallopian tubes, ovaries</td>
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<tr>
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<td></td>
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<tr>
<td>Modified Radical Hysterectomy (type 2)</td>
<td>Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterovesical ligaments and upper 1-2 cm vagina</td>
</tr>
<tr>
<td>Radical Hysterectomy (type 3)</td>
<td>Uterus, cervix, upper 1/3-1/2 vagina, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum)</td>
</tr>
</tbody>
</table>

Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

<table>
<thead>
<tr>
<th>With Secondary Sexual Development</th>
<th>Without Secondary Sexual Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal breast and pelvic development</td>
<td>Normal breast, abnormal uterine development</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Androgen insensitivity</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Anatomic abnormalities</td>
</tr>
<tr>
<td>PCOS</td>
<td>Müllerian agenesis, urothelial septum, imperforate hymen</td>
</tr>
<tr>
<td>Hypothalamic dysfunction</td>
<td>Uterine fibroids</td>
</tr>
<tr>
<td></td>
<td>Endometriosis</td>
</tr>
<tr>
<td></td>
<td>Adenomyosis</td>
</tr>
<tr>
<td></td>
<td>Menorrhagia</td>
</tr>
<tr>
<td></td>
<td>DUB</td>
</tr>
<tr>
<td></td>
<td>High FSH (hypergonadotropic hypogonadism)</td>
</tr>
<tr>
<td></td>
<td>Gonadal dysgenesis</td>
</tr>
<tr>
<td></td>
<td>• Abnormal sex chromosome (Turner’s XO)</td>
</tr>
<tr>
<td></td>
<td>Normal sex chromosome (46XX, 46XY)</td>
</tr>
<tr>
<td></td>
<td>Constitutional delay (most common)</td>
</tr>
<tr>
<td></td>
<td>Congenital abnormalities</td>
</tr>
<tr>
<td></td>
<td>• Isolated GnRH deficiency</td>
</tr>
<tr>
<td></td>
<td>• Pituitary failure (Kallman syndrome, neonatal injury, pituitary adenoma, etc.)</td>
</tr>
<tr>
<td></td>
<td>Acquired</td>
</tr>
<tr>
<td></td>
<td>• Endocrine disorders (type 1 DM)</td>
</tr>
<tr>
<td></td>
<td>• Pituitary tumors</td>
</tr>
<tr>
<td></td>
<td>• Systemic disorders (IBD, JRA, chronic infections, etc.)</td>
</tr>
<tr>
<td>Low FSH (hypogonadotropic hypogonadism)</td>
<td>Primary Amenorrhea</td>
</tr>
<tr>
<td></td>
<td>No menses by age 13 in absence of 2º sexual characteristics or no menses by age 15 with 2º sexual characteristics or no menses 2 yr after thelarche</td>
</tr>
<tr>
<td>Primary Amenorrhea</td>
<td>Secondary Amenorrhea</td>
</tr>
<tr>
<td></td>
<td>No menses for &gt;6 mo or 3 cycles after documented menarche</td>
</tr>
<tr>
<td>Oligomenorrhea</td>
<td>Episodic vaginal bleeding occurring at intervals &gt;35 d</td>
</tr>
</tbody>
</table>
Table 3. Differential Diagnosis of Secondary Amenorrhea

<table>
<thead>
<tr>
<th>With Hyperandrogenism</th>
<th>Without Hyperandrogenism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>Hypergonadotropic hypogonadism (i.e. premature ovarian failure: high FSH, low estradiol)</td>
</tr>
<tr>
<td>Autonomous hyperandrogenism (androgen secretion independent of the HPO axis)</td>
<td></td>
</tr>
<tr>
<td>Ovarian: tumor, hyperthecosis</td>
<td>• Idiopathic</td>
</tr>
<tr>
<td>Adrenal androgen-secreting tumor</td>
<td>• Autoimmune: type 1 DM, autoimmune thyroid disease, Addison’s disease</td>
</tr>
<tr>
<td>Late onset or mild congenital adrenal hyperplasia (rare)</td>
<td>• Iatrogenic: cyclophosphamide drugs, radiation</td>
</tr>
<tr>
<td></td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td></td>
<td>Endocrinopathies: most commonly hyper or hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>• Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic</td>
</tr>
<tr>
<td></td>
<td>hypophysitis, infiltration (sarcoidosis), head injury, Sheehan’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or</td>
</tr>
<tr>
<td></td>
<td>anorexia)</td>
</tr>
</tbody>
</table>

| Hypergonadotropic hypogonadism (i.e. premature ovarian failure: high FSH, low estradiol) |                                                                                         |
|                                                                                      |                                                                                         |
| β-hCG maximum elevation in pregnancy is >50 ng/dL                                    |                                                                                         |
| β-hCG by 72h is >100 ng/dL                                                          |                                                                                         |
| CT head is normal                                                                  |                                                                                         |
| MRI hypothalamus, pituitary                                                         |                                                                                         |
| Measure other pituitary hormones                                                    |                                                                                         |
| Common etiology:                                                                   |                                                                                         |
| • Weight loss                                                                       |                                                                                         |
| • Excessive exercise                                                                |                                                                                         |
| • Systemic diseases                                                                 |                                                                                         |
| PCOS – hyperandrogenism                                                             |                                                                                         |
| Premature ovarian failure                                                            |                                                                                         |
| HP axis dysfunction                                                                 |                                                                                         |
| MRI hypothalamus, pituitary                                                         |                                                                                         |
| Measure other pituitary hormones                                                    |                                                                                         |
| Common etiology:                                                                   |                                                                                         |
| • Weight loss                                                                       |                                                                                         |
| • Excessive exercise                                                                |                                                                                         |
| • Systemic diseases                                                                 |                                                                                         |
| Functional hypothalamic amenorrhea is the most common cause of secondary amenorrhea |                                                                                         |

Investigations

- β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
- progesterone challenge to assess estrogen status
  - medroxyprogesterone acetate (Provera®) 10 mg PO OD for 10-14 d
  - any uterine bleed within 2-7 d after completion of Provera® is considered to be a positive test/withdrawal bleed
    - withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progesterone results in bleeding
    - if no bleeding occurs, there may be inadequate estrogen (hypoestrogenism) or excessive androgens or progesterones (decidualization)
- karyotype: indicated if premature ovarian failure or absent puberty
- U/S to confirm normal anatomy, identify PCOS
### Treatment

Table 4. Management of Amenorrhea

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1º AMENORRHEA</strong></td>
<td></td>
</tr>
<tr>
<td>AIS</td>
<td>• Gonadal resection after puberty</td>
</tr>
<tr>
<td>• Psychological counseling</td>
<td></td>
</tr>
<tr>
<td>• Creation of neo-vagina</td>
<td></td>
</tr>
<tr>
<td>Anatomical</td>
<td>• Surgical management</td>
</tr>
<tr>
<td>• Imperforate hymen</td>
<td></td>
</tr>
<tr>
<td>• Transverse vaginal septum</td>
<td></td>
</tr>
<tr>
<td>• Cervical agenesis</td>
<td></td>
</tr>
<tr>
<td>Müllerian dysgenesis (MRKH syndrome)</td>
<td>• Psychological counseling</td>
</tr>
<tr>
<td>• Creation of neo-vagina with dilation</td>
<td></td>
</tr>
<tr>
<td>• Diagnostic study to confirm normal urinary system and spine</td>
<td></td>
</tr>
<tr>
<td><strong>2º AMENORRHEA</strong></td>
<td></td>
</tr>
<tr>
<td>Uterine defect</td>
<td>• Evaluation with hysterosalpingography or sonohysterography</td>
</tr>
<tr>
<td>• Asherman’s syndrome</td>
<td>• Hysteroscopy: excision of synchieae</td>
</tr>
<tr>
<td>HP-axis dysfunction</td>
<td>• Identify modifiable underlying cause</td>
</tr>
<tr>
<td>• Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development (NOT proven to work)</td>
<td></td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td>• Screen for DM, hypothyroidism, hyperparathyroidism, hypocricaltism</td>
</tr>
<tr>
<td>• Hormonal therapy with estrogen + progestin to decrease risk of osteoporosis; can use OCP</td>
<td></td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>• MRI/CT head to rule out lesion</td>
</tr>
<tr>
<td>• If no demonstrable lesions by MRI:</td>
<td>• Bromocriptine, cabergoline if fertility desired</td>
</tr>
<tr>
<td>• Combined OCPs if no fertility desired</td>
<td>• Demonstrable lesions by MRI: surgical management</td>
</tr>
<tr>
<td>Polycystic ovarian syndrome</td>
<td>• See Polycystic Ovarian Syndrome, GY22</td>
</tr>
</tbody>
</table>

### Abnormal Uterine Bleeding

**Abnormal Uterine Bleeding** change in frequency, duration, or amount of menstrual flow.

- **Gynecological**
  - Menorrhagia: Hormone imbalance, Fibroids/Leiomyomata, Uterine polyps, Adenomyosis, Copper IUD
  - Metrorrhagia/Menometrorrhagia: Trauma, sexual abuse, foreign body infection: endometritis, cervicitis, vaginitis, STD
  - Benign growths: uterine, cervical, vaginal
  - Pregnancy-related: Weight loss, excess exercise, stress
  - PCOS
  - DUB (diagnosis of exclusion)

- **Non-gynecological**
  - Endocrine: Hyper/hypothyroidism, Adrenal insufficiency
  - Insulin resistance (PCOS), Prolactinoma
  - Blood Dyscrasias: Coagulopathy (vWD), Platelet abnormalities (ITP), Leukemia
  - Hematologic malignancy
  - Renal Failure: Impaired estrogen excretion
  - Drugs: Anticoagulants, Danazol, OCP, HRT (breakthrough bleed), Spironolactone, Steroids, Chemotherapy, Neuroleptics
  - Hepatic Disease: Impaired estrogen metabolism

**Figure 10. Approach to abnormal uterine bleeding**

**Causal Conditions**
- pre-menarchal
  - trauma, sexual abuse
- pre-menopausal
  - ovulatory (see Table 5)
  - anovulatory (see Table 5)
- pregnancy-related
- post-menopausal
  - genital tract disease
    - atrophy
    - neoplasms
  - systemic disease
  - drugs
    - HRT
    - anti-coagulants

**Abnormal Uterine Bleeding** Determine if patient is hemodynamically stable prior to any other task.

**Hepatic Disease** Impaired estrogen metabolism (caused by factors).

**AUB in women >40 yr requires an endometrial biopsy to rule out cancer even if known to have fibroids**
Table 5. Comparison of Anovulatory and Ovulatory Abnormal Uterine Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Anovulatory</th>
<th>Ovulatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Definition</td>
<td>Unpredictable endometrial bleeding of variable flow and duration; sex steroids are produced but not cyclically, resulting in irregular bleeding</td>
<td>Typically cyclic, but heavy or prolonged</td>
</tr>
<tr>
<td>Etiology</td>
<td>PCOS</td>
<td>Anatomic or physical lesion (e.g. polyp, fibroid, adenomyosis, neoplasm, foreign body)</td>
</tr>
<tr>
<td></td>
<td>Thyroid dysfunction</td>
<td>Hemostatic defect</td>
</tr>
<tr>
<td></td>
<td>Elevated prolactin levels</td>
<td>Infection; trauma</td>
</tr>
<tr>
<td></td>
<td>Rare estrogen-producing tumors</td>
<td>Local disturbances in prostaglandins (elevated endometrial vasodilatory prostaglandin, decreased vasoconstrictive prostaglandin)</td>
</tr>
<tr>
<td></td>
<td>Stress, weight loss, exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver and kidney disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Structural disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medication side effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Estrogen-dependent breakthrough bleeding: chronic estrogen production unopposed by adequate progesterone production → continued proliferation of the endometrium → thickened endometrium outgrows its blood supply → focal necrosis with partial shedding not uniformly → bleeding is usually irregular, prolonged, and heavy</td>
<td>Depends on underlying etiology</td>
</tr>
</tbody>
</table>

**Investigations**

- vitals ± orthostatic vitals
- CBC, serum ferritin
- β-hCG to rule out pregnancy
- TSH, free T₁
- coagulation profile (especially in adolescents): rule out von Willebrand’s disease
- prolactin if amenorrheic
- FSH, LH
- serum androgens (especially free testosterone)
- day 21 (luteal phase) progesterone to confirm ovulation
- Pap test
- pelvic U/S: detect polyps, fibroids, measure endometrial thickness (postmenopausal)
- SHG: very sensitive for intruterine pathology (polyps, submucous fibroids)
- HSG
- endometrial biopsy: consider biopsy in women >40 yr
  - must do endometrial biopsy in all women presenting with postmenopausal bleeding to exclude endometrial cancer
- D&C: not for treatment; diagnosis only (usually with hysteroscopy)

**Treatment**

- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider DUB
  - medical
    - mild DUB
      - NSAIDs
      - anti-fibrinolytic (e.g. Cyklokapron*) at time of menses
      - combined OCP
      - progestins (“Provera”) on first 10-14 d of each mo or every 3 mo if oligomenorrheic
      - Mirena* IUD
      - danazol
    - acute, severe DUB
      - replace fluid losses, consider admission
        - a) estrogen (Premarin*) 25 mg IV q4h x 24 h with dimenhydrinate 50 mg IV/PO q4h or anti-fibrinolytic (e.g. Cyklokapron*) 10 mg/kg IV q8h
        - b) any OCP with minimum 50 µg estradiol 1 tab PO q4h x 24 h with dimenhydrinate 50 mg IV/PO q4h
          - taper to 1 tab tid x 2 d → bid x 2 d → OD
          - after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
      - clomiphene citrate
        - consider in patients who are anovulatory and who wish to get pregnant
      - surgical
        - endometrial ablation; consider pretreatment with danazol or GnRH agonists
          - if finished childbearing
          - repeat procedure may be required if symptom reoccur especially if <40 yr
        - hysterectomy: definitive treatment

**Dysfunctional Uterine Bleeding**

Abnormal bleeding not attributable to organic (anatomic/systemic) disease; DUB is a diagnosis of exclusion; anovulatory AUB often used synonymously with DUB.
**Dysmenorrhea**

**Etiology**
- see Differential Diagnoses of Common Presentations, GY6

**Table 6. Comparison of Primary and Secondary Dysmenorrhea**

<table>
<thead>
<tr>
<th>Features</th>
<th>Primary Dysmenorrhea</th>
<th>Secondary Dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual pain in absence of organic disease Begins 6 mo-2 yr after menarche (once ovulatory cycles established)</td>
<td>Menstrual pain due to organic disease Usually begins in women who are in their 20s, worsens with age May improve temporarily after childbirth</td>
<td></td>
</tr>
<tr>
<td>Signs and Symptoms</td>
<td>Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated)</td>
<td>Associated dyspareunia, abnormal bleeding, infertility</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Associated dyspareunia, abnormal bleeding, infertility Rule out underlying pelvic pathology and confirm cyclic nature of pain</td>
<td>Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women &lt;20 yr) U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis Screening for infections (vaginal and cervical cultures) and Papanicolaou smear may be required</td>
</tr>
<tr>
<td>Treatment</td>
<td>PG synthetase inhibitors (e.g. Anaprox®) should be started before onset of pain OCP: suppress ovulation/reduce menstrual flow</td>
<td>Treat underlying cause</td>
</tr>
</tbody>
</table>

**Endometriosis**

**Etiology**
- not fully understood
- proposed mechanisms (combination likely involved)
  - retrograde menstruation (Sampson’s theory)
    - seeding of endometrial cells by transtubal regurgitation during menstruation
    - endometrial cells most often found in dependent sites of the pelvis
  - immunologic theory: altered immunity may limit clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
    - undefined endogenous biochemical factor may induce undifferentiated peritoneal cells to develop into endometrial tissue
  - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

**Epidemiology**
- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 yr
- regresses after menopause

**Risk Factors**
- family history (7-10x increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – resolve with treatment of anomaly
- nulliparity
- age >25 yr

**Sites of Occurrence**
- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicoperitoneal fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs
Clinical Features
• may be asymptomatic
• history
  • menstrual symptoms
  • cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
  • secondary dysmenorrhea
  • sacral backache with menses
  • pain may eventually become chronic, worsening perimenstrually
  • premenstrual and postmenstrual spotting
  • deep dyspareunia
• infertility
  • 30-40% of patients with endometriosis will be infertile
  • 15-30% of those who are infertile will have endometriosis
• bowel and bladder symptoms
  • frequency, dysuria, hematuria
  • diarrhea, constipation, hematochezia, dyschezia
• physical
  • tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
  • fixed retroversion of uterus
  • firm, fixed adnexal mass (endometrioma)
  • physical findings not present in adolescent population

Investigations
• definitive diagnosis requires
  • direct visualization of lesions typical of endometriosis at laparoscopy
  • biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)
  • laparoscopy
  • mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  • endometrioma: “chocolate” cysts on the ovaries
  • “powder-burn” lesions on the peritoneal surface
  • early white lesions and clear blebs
  • peritoneal “pockets”
• CA-125
• may be elevated in patients with endometriosis

Treatment
• depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)
• medical
  • NSAIDs (e.g. naproxen sodium – Anaprox®)
  • pseudopregnancy
    • cyclic/continuous estrogen-progesterin (OCP)
    • medroxyprogesterone (Depo-Provera®)
  • dienogest (Natazia®)
  • pseudomenopause
  • 2nd line: only short-term (<6 mo) due to osteoporotic potential with prolonged use, unless combined with add-back therapy (e.g. estrogen/progesterone or SERM); if long-term use required, add-back estrogen+progesterone
  • danazol (Danocrine®): weak androgen
    – side effects: weight gain, fluid retention, acne, hirsutism, voice change
  • leuprolide (Lupron®): GnRH agonist (suppresses pituitary)
    – side effects: hot flashes, vaginal dryness, reduced libido
    – can use ≥12 mo with add-back progestin or estrogen
• surgical
  • conservative laparoscopy using laser, electrocautery ± laparotomy
  • ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
  • definitive: bilateral salpingo-oophorectomy ± hysterectomy
  • ± follow-up with medical treatment for pain control not shown to impact on preservation of fertility
  • best time to become pregnant is immediately after conservative surgery

There may be little correlation between the extent of endometriosis and symptomatology

Classic Triad of Endometriosis
• Dysmenorrhea
  • Dyspareunia (cul-de-sac, uterosacral ligament)
• Dyschezia (uterosacral ligament, cul-de-sac, recto-sigmoid attachment)

A sharp, firm, and exquisitely tender “bark” on the uterosacral ligament is a classic feature of endometriosis

Laparoscopic Surgery for Endometriosis
Cochrane Databse of Systematic Reviews 2014:CD011031

Purpose: To assess the effectiveness and safety of laparoscopic surgery for the treatment of painful symptoms and infertility associated with endometriosis.

Selection Criteria: RCTs in which effectiveness and safety of laparoscopic surgery was compared with any other laparoscopic or robotic intervention, holistic or medical treatment, or diagnostic laparoscopy only.

Results: 10 RCTs, 973 participants. Laparoscopic surgery was associated with increased overall pain compared with diagnostic laparoscopy at 6 and 12 mo (OR 5.6, 95% CI 3.31-9.31; OR 10.00, 95% CI 3.21-31.17). Laparoscopic surgery was also associated with increased pregnancy rate compared with diagnostic laparoscopy (OR 1.94, 95% CI 1.20-3.16) and increased pregnancy rate (OR 1.94, 95% CI 1.29-2.80). Compared to diagnostic laparoscopy plus medical therapy (GnRHa plus add-back therapy), laparoscopic ablation resulted in a greater number of participants reporting no pain at 12 mo (OR 5.63, 95% CI 1.18-26.85) although there was no difference in overall/pain relief at 12 mo comparing laparoscopic ablation to laparoscopic excision.

Conclusions: Moderate quality evidence suggests that laparoscopic surgery to treat mild and moderate endometriosis reduces overall pain and increases live birth and ongoing pregnancy rates. There was insufficient evidence on adverse events to allow any conclusions regarding safety.

Endometriosis is classified according to a scoring system standardized by the American Society for Reproductive Medicine; score is based on location and extent of disease

Recurrent Rates
Medical therapy: 30-50%
Conservative surgery: 14-40%
Adenomyosis

- synonym: "endometriosis interna" (uterine wall may be diffusely involved)

Epidemiology
- 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
- mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
- adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features
- often asymptomatic
- menorrhagia, secondary dysmenorrhea, pelvic discomfort
- dyspareunia, dyschezia
- uterus symmetrically bulky, usually <14 cm, mobility not restricted, no associated adnexal pathology
- Halban sign: tender, softened uterus on premenstrual bimanual exam

Investigations
- clinical diagnosis
- U/S or MRI can be helpful
- endometrial sampling to rule out other pathology

Treatment
- iron supplements as necessary
- analgesics, NSAIDs
- OCP, medroxyprogesterone (Depo-Provera°)
- low dose danazol 100-200 mg PO OD (trial x 4 mo)
- GnRH agonists (e.g. leuprolide)
- definitive: hysterectomy (no conservative surgical treatment)

Leiomyomata (Fibroids)

Epidemiology
- diagnosed in approximately 40-50% of pre-menopausal women >35 yr
- more common in African Americans, where they are also larger and occur at earlier age
- common indication for major surgery in females
- minimal malignant potential (1:1,000)
- typically regress after menopause; enlarging fibroids in a postmenopausal woman should prompt consideration of malignancy
  - 50% of leiomyosarcomas originate from within fibroids

Pathogenesis
- estrogen stimulates monoclonal smooth muscle proliferation
- progesterone stimulates production of proteins that inhibit apoptosis
- degenerative changes (occur when tumor outgrows blood supply)
  - hyaline degeneration (most common degenerative change)
  - cystic degeneration (from breakdown of hyaline)
  - red/carneous degeneration (hemorrhage into tumor, may occur in pregnancy)
  - fatty degeneration
  - calcification
  - sarcomatous degeneration (rare)
  - parasitic myoma: tumor becomes attached to another organ (typically omentum or small bowel mesentery), develops new blood supply and loses connection to uterus

Clinical Features
- majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
- abnormal uterine bleeding (30%): dysmenorrhea, menorrhagia
- pressure/bulk symptoms (20-50%)
  - pelvic pressure/heaviness
  - increased abdominal girth
  - urinary frequency and urgency
  - acute urinary retention (extremely rare but surgical emergency!)
  - constipation, bloating (rare)
- acute pelvic pain
  - fibroid degeneration
  - dyspareunia, dyschezia
  - fibroid torsion (pedunculated subserosal)

Adenomyosis

- Extension of areas of endometrial glands and stroma into the myometrium

Final diagnosis of adenomyosis is based on pathologic findings, but predictably identified on MRI

Leiomyomata/Fibroids

- Benign smooth muscle tumor of the uterus (most common gynecological tumor)
- Submucosal leiomyomata are most symptomatic (bleeding, infertility)
- AUB in women >40 yr requires an endometrial biopsy to rule out cancer even if known to have fibroids

Figure 11. Possible anatomic locations of uterine leiomyomata
• infertility, recurrent pregnancy loss
• pregnancy complications (potential enlargement and increased pain, obstructed labor, difficult C-section)

**Investigations**
• bimanual exam: uterus asymmetrically enlarged, usually mobile
• CBC: anemia
• U/S: to confirm diagnosis and assess location of fibroids
• sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or if intracavitary growth
• endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 yr)
• occasionally MRI is used for pre-operative planning (e.g. before myomectomy)

**Treatment**
• only if symptomatic, rapidly enlarging, menorrhagia, menometrorrhagia, intracavitary
• treat anemia if present
• only if symptomatic, rapidly enlarging, menorrhagia, menometrorrhagia
• occasionally MRI is used for pre-operative planning (e.g. before myomectomy)
• U/S: to confirm diagnosis and assess location of fibroids
• CBC: anemia
• bimanual exam: uterus asymmetrically enlarged, usually mobile

*Contraception*

**Table 7. Classification of Contraceptive Methods**

<table>
<thead>
<tr>
<th>Type</th>
<th>Effectiveness (perfect use, typical use)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological</strong></td>
<td></td>
</tr>
<tr>
<td>Withdrawal/coitus interrupt</td>
<td>77%</td>
</tr>
<tr>
<td>Rhythym method/calender/mucus/symptothermal</td>
<td>98%, 76%</td>
</tr>
<tr>
<td>Lactational amenorrhoea</td>
<td>98% (first 6 mo postpartum)</td>
</tr>
<tr>
<td>Chance – no method used</td>
<td>10%</td>
</tr>
<tr>
<td>Abstinence of all sexual activity</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Barrier Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Condom alone</td>
<td>98%, 85%</td>
</tr>
<tr>
<td>Sponge alone</td>
<td>82%, 71%</td>
</tr>
<tr>
<td>Sponge – Parous</td>
<td>80%, 68%</td>
</tr>
<tr>
<td>– Nulliparous</td>
<td>91%, 84%</td>
</tr>
<tr>
<td>Diaphragm with spermicide</td>
<td>94%, 84%</td>
</tr>
<tr>
<td>Female condom</td>
<td>95%, 79%</td>
</tr>
<tr>
<td>Cervical cap – Parous</td>
<td>74%, 68%</td>
</tr>
<tr>
<td>– Nulliparous</td>
<td>91%, 84%</td>
</tr>
</tbody>
</table>

*Infertility, recurrent pregnancy loss*
Table 7. Classification of Contraceptive Methods (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Effectiveness (perfect use, typical use)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal</td>
<td></td>
</tr>
<tr>
<td>OCP</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Nuva Ring®</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Transdermal (Ortho Evra®)</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Depo-Provera®</td>
<td>99.7%, 97%</td>
</tr>
<tr>
<td>Progestin-only pill (Micronor®)</td>
<td>90-99%</td>
</tr>
<tr>
<td>Mirena® IUD</td>
<td>99.9%</td>
</tr>
<tr>
<td>Subdermal implant (Neplanon/Implanon®)</td>
<td>99.9%</td>
</tr>
<tr>
<td>Copper IUD</td>
<td>99.3%</td>
</tr>
<tr>
<td>Surgical</td>
<td></td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>99.65%</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>99.9%</td>
</tr>
<tr>
<td>Emergency Postcoital Contraception (EPC)</td>
<td></td>
</tr>
<tr>
<td>“Plan B” levonorgestrel only</td>
<td>98% (within 24 h), decreases by 30% at 72 h</td>
</tr>
<tr>
<td>Postcoital IUD</td>
<td>98% (within 24 h), decreases by 70% at 72 h</td>
</tr>
</tbody>
</table>

Effectiveness: percentage of women reporting no pregnancy after 1 yr of use.

Hormonal Methods

Combined Oral Contraceptive Pills
- most contain low dose ethinyl estradiol (20-35 µg) plus progestin (norethindrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

Transdermal (Ortho Evra®)
- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive wk (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

Contraceptive Ring (Nuva Ring®)
- thin flexible plastic ring; releases etonogestrel 120 µg/d and estradiol 15 µg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- avoids first pass effect
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

Starting Hormonal Contraceptives
- thorough history and physical exam, including blood pressure and breast exam
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam not required as STD screening can be done by urine and pap smear screening does not start until >21 yr


Rates of Venous Thromboembolism (VTE: DVT and PE) expressed in women/yr
- Non-users of reproductive age: 4-6/10,000
- OCP users*: 9-10/10,000
- Pregnancy: 28/10,000
- Immediate post-partum: 300-400/10,000

*Risk is highest in the first months of use and in medication switch.

Effect of Ethinyl Estradiol Dose
- ALL OCPs with ~35 µg ethinyl estradiol carry a lower risk of VTE compared with oral contraceptives with 50 µg.

Effect of Progestin Type
- Drospirenone: third generation progestin, e.g. “foostrin®” and “pop®”
- Levonorgestrel: second generation progestin, e.g. “Alesse®”

Two high quality research studies found comparable VTE rates with drospirenone-containing OCPs and other approved products.
1. Dinger et al., Contraception 2007;76:244-254
2. Seeger et al., Obstet Gynecol 2007;110:587-593

Two reports with significant methodological flaws found increased VTE risk. Results and conclusions may have been distorted by residual confounding.
1. Lidegaard et al., BMJ 2009;339:b2920
2. Van Hylckama Vlieg et al., BMJ 2009;339:b2921

Conclusion
- Occurrence of serious risks, such as VTE, is rare with all contemporary OCPs.
- Individualized risk assessment is mandatory.
- For most healthy women of reproductive age, the benefits of OCPs will outweigh the risks.

Risk of Non-Fatal Venous Thromboembolism in Women Using Oral Contraceptives Containing Drospirenone Compared with Women Using Oral Contraceptives Containing Levonorgestrel: A Case-Control Study Using United States Claims Data
BMJ 2011;342:d2325

Study: Nested case-control cohort study.
- Patients: Women aged 15-44 yr receiving oral contraceptives.
- Intervention: Drospirenone-containing contraceptive vs. levonorgestrel-containing contraceptive.
- Outcome: Non-fatal venous thromboembolism.
- Results: Women receiving drospirenone-containing oral contraceptives were two times as likely to develop non-fatal VTE compared to women receiving levonorgestrel-containing contraceptives (age adjusted incidence rate ratio was 2.8).
Table 8. Combined Estrogen and Progestin Contraceptive Methods

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Advantages</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ovulatory suppression through inhibition of LH and FSH</td>
<td>• Highly effective</td>
<td>• Estrogen-related</td>
<td>• Known/suspected pregnancy</td>
</tr>
<tr>
<td>• Decidualization of endometrium</td>
<td>• Reversible</td>
<td>• Breast changes (tenderness, enlargement)</td>
<td>• Undiagnosed abnormal vaginal bleeding</td>
</tr>
<tr>
<td>• Thickening of cervical mucus resulting in decreased sperm penetration</td>
<td>• Cycle regulation</td>
<td>• Fluid retention/bloating/edema</td>
<td>• Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis</td>
</tr>
<tr>
<td></td>
<td>• Decreased dysmenorrhea and menorrhagia (less anemia)</td>
<td>• Weight gain (rare)</td>
<td>• Cerebrovascular or coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>• Decreased benign breast disease and ovarian cyst development</td>
<td>• Migraine, headaches</td>
<td>• Estrogen-dependent tumors (breast, uterus)</td>
</tr>
<tr>
<td></td>
<td>• Decreased risk of ovarian and endometrial cancer</td>
<td>• Thromboembolic events</td>
<td>• Impaired liver function associated with acute liver disease</td>
</tr>
<tr>
<td></td>
<td>• Increased cervical mucus which may lower risk of STDs</td>
<td>• Liver adenoma (rare)</td>
<td>• Congenital hyperlipidemias</td>
</tr>
<tr>
<td></td>
<td>• Decreased PMS symptoms</td>
<td>• Breakthrough bleeding (low estradiol levels)</td>
<td>• Smoker age &gt;35 yr</td>
</tr>
<tr>
<td></td>
<td>• Improved acne</td>
<td></td>
<td>• Migraines with focal neurological symptoms (excluding aura)</td>
</tr>
<tr>
<td></td>
<td>• Osteoporosis protection (possibly)</td>
<td></td>
<td>• Uncontrolled HTN</td>
</tr>
</tbody>
</table>

Reference: World Health Organization Guidelines for Oral Contraceptive Pill Use

Table 9. Selected Examples of OCPs

<table>
<thead>
<tr>
<th>Type</th>
<th>Active Compounds (estriol and progestin derivative)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alesse®</td>
<td>• 20 µg ethinyl estradiol and 0.5 mg levonorgestrel</td>
<td>• Low dose (20 µg) OCP</td>
<td>• Low-dose pills can often result in breakthrough bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Can improve acne and help regulate menstrual cycles</td>
<td>• If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content</td>
</tr>
</tbody>
</table>

Tri-cyclen® | • 35 µg ethinyl estradiol and 0.180/0.215/0.250 mg norgestimate | • Low androgenic activity can help with acne | • Triphasic OCPs should not be used continuously (unlike monophasic formulations), although should be used continuously for 1 pack |
| | • Triphasic oral contraceptive (graduated levels of progestrone) | | • Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency) |
| Yasmin® and Yaz® | • Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin) | • Decreased perception of cyclic weight gain/bloating | • Check potassium if patient also on ACE inhibitor; ARB, K+-sparring diuretic, heparin |
| | • Yaz®: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4-d pill (4 d pill free interval) | • Fewer PMS symptoms | • Continue use of spironolactone |
| | • Drospirenone has antimineralocorticoid activity and antiandrogenic effects | • Improved acne | • Increased risk of DVT-PE |

PROGESTIN-ONLY METHOD

Table 10. Progestin Only Contraceptive Methods

<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suitable for postpartum women (does not affect breast milk supply)</td>
<td>• Progestin prevents LH surge</td>
<td>• Irregular menstrual bleeding</td>
<td>• Absolute</td>
</tr>
<tr>
<td>• Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease)</td>
<td>• Thickening of cervical mucus</td>
<td>• Weight gain</td>
<td>• None</td>
</tr>
<tr>
<td>• Women intolerant of estrogenic side effects of combined OCPs</td>
<td>• Decrease tubal motility</td>
<td>• Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Endometrial decidualization</td>
<td>• Breast tenderness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs</td>
<td>• Mood changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Functional ovarian cysts</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acne/oily skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hirsutism*</td>
<td></td>
</tr>
</tbody>
</table>

Absolute

- Known/suspected pregnancy
- Undiagnosed abnormal vaginal bleeding
- Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis
- Cerebrovascular or coronary artery disease
- Estrogen-dependent tumors (breast, uterus)
- Impaired liver function associated with acute liver disease
- Congenital hyperlipidemia
- Smoker age >35 yr
- Migraines with focal neurological symptoms (excluding aura)
- Uncontrolled HTN

Relative

- Migraines (non-focal with aura <1 h)
- DM complicated by vascular disease
- SLE
- Controlled HTN
- Hyperlipidemia
- Sickle cell anemia
- Gallbladder disease

Drug Interactions/Risks

- Rifampin, phenobarbital, phenytoin, and primidone can decrease efficacy, requiring use of back-up method
- No evidence of fetal abnormalities if conceived on OCP
- No evidence that OCP is harmful to nursing infant but may decrease milk production; not recommended until 6 wk postpartum, ideally until 3 mo postpartum

 irr Regular breakthrough bleeding often occurs in the first few months after starting OCP, usually resolves after three cycles

 irr Missed Combined OCPs

- Miss 1 pill in <24 h
  - Take 1 pill ASAP and the next pill at the usual time
- Miss >1 pill in a row in first wk
  - Take 1 pill ASAP and continue taking one pill daily until the end of the pack
  - Use back-up contraception for 7 d; EPC may be necessary
- Miss <3 pills in 2nd or 3rd wk of cycle
  - Take 1 pill ASAP and continue taking one pill daily until the end of the pack
  - Do not take placebo (21-d packs) or do not take a hormone free interval (21-d packs)
  - Start the next pack immediately after finishing the previous one
  - No need for back-up contraception
- Miss ≥3 pills during the 2nd or 3rd wk
  - Take 1 pill ASAP and continue taking one pill daily until the end of the pack
  - Do not take placebo (21-d packs) or do not take a hormone free interval (21-d packs)
  - Start the next pack immediately after finishing the previous one
  - Use back-up contraception for 7 d; EPC may be necessary

Nexplanon is the second generation model which contains barium sulfate to make it radio-opaque so its position can be visualized by x-ray if unable to palpate the rod to remove it.

Depo-Provera®
• injectable depot medroxyprogesterone acetate
dose 150 mg IM q12-14wk (convenient dosing)
initiate within 5 d of beginning of normal menses, immediately postpartum in breastfeeding and non-breastfeeding women
irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
highly effective 99%; failure rate 0.3%
side effect: decreased bone density (may be reversible)
disadvantage: restoration of fertility may take up to 1-2 yr

Nexplanon/Implanon®
• subdermal contraceptive rod
contains 68 mg of etonogestrel, released at a rate of 25-30 µg per d
inserted subdermally into the inner side of the non-dominant upper arm
highly effective 99%; failure rate 0.3%
side effect: decreased bone density (may be reversible)
disadvantage: restoration of fertility may take up to 1-2 yr

Disadvantage: restoration of fertility may take up to 1-2 yr

Absolute
• Both Copper and Progestrone IUD
Known or suspected pregnancy
Undiagnosed genital tract bleeding
Acute or chronic PID
Lifestyle risk for STDs*
Copper IUD:
Known allergy to copper
Wilson’s disease
Relative
• Both Copper and Progestrone IUD
Malignant heart disease
Past history of PID or ectopic pregnancy
Presence of prosthesis
Abnormalities of uterine cavity, intracavitary fibroids
Cervical stenosis
Immune suppressed individuals (e.g. HIV)
Copper IUD: severe dysmenorrhea or menorrhagia

Cervical swabs for gonorrhea and chlamydia should be done prior to IUD insertion.

Depot Medroxyprogesterone Acetate and Bone Effects
ACOG Committee Opinion 415, 2006
Obstet Gynecol 2006;108:727-730
• The effect of DMPA on BMD should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive yr.
• The greatest loss of BMD occurs in the first 1-2 yr of DMPA use.
• Contraceptive implants and intrauterine devices that do not affect BMD should be considered as first-line for adolescents.
• Inform patients about benefits and the potential risks of DMPA, and encourage daily exercise, calcium and vitamin D intake.
• Routine BMD monitoring is not recommended for DMPA users.

Steroidal Contraceptives and Bone Fractures in Women: Evidence from Observational Studies
Cochrane DB Syst Rev 2003;3:CD004695
Background: Steroidal contraceptives have been associated with effects on bone mineral density (BMD) in women.
Study: Systematic review of observational studies of comparisons of hormonal contraceptive with nonhormonal contraceptive, no contraceptive, or other hormonal contraceptive on bone density.
Results: 7 case-control and 7 cohort studies were included.
• One study reported increased fracture risk for depot medroxypregesterone acetate (DMPA) ever-use (OR 1.44), >4 yr use (OR 2.16).
• One study reported decreased fracture risk for continuous use (OR 0.79) and longer use of hormonal IUD.

Continuous or Extended Cycle vs. Cyclic Use of Combined Oral Contraceptives for Contraception
Cochrane DB Syst Rev 2005;3:CD004869
Background: The efficacy and side effects of cyclic administration vs. extended use (longer periods of active pills and/or shorter periods placebo) or continuous use (uninterrupted active pill administration) of combined oral contraceptives (COC) are unclear.
Study: Systematic review of randomized clinical trials comparing continuous or extended vs. cyclic COC administration.
Findings: Eight RCTs met inclusion criteria.
• No difference in efficacy of pregnancy prevention.
• No difference in compliance with dosing schedules.
• Extended cycle use lowered prevalence of menstrual symptoms (e.g. headaches, pain, fatigue).
Emergency Postcoital Contraception

### Table 12. Emergency Contraceptive Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HORMONAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yuzpe Method</td>
<td>• Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d</td>
<td>• Unknown; theories include:</td>
<td>• Pre-existing pregnancy (although not teratogenic)</td>
</tr>
<tr>
<td></td>
<td>• Oral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg/levonorgestrel 500 µg)</td>
<td>• Suppresses ovulation or causes deficient luteal phase</td>
<td>• Caution in women with contraindications to OCP (although NO absolute contraindications)</td>
</tr>
<tr>
<td></td>
<td>• Can substitute with any OCP as long as same dose of estrogen used</td>
<td>• Alters endometrium to prevent implantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2% overall risk of pregnancy</td>
<td>• Affects sperm/ova transport</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Efficacy decreased with time (e.g. less effective at 72 h than 24 h)</td>
<td>• Nausea (due to estrogen; treat with dimenhydrinate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Irregular spotting</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pre-existing pregnancy (although not teratogenic)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Caution in women with contraindications to OCP (although NO absolute contraindications)</td>
</tr>
<tr>
<td>“Plan B”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Consists of levonorgestrel 750 µg q12h for 2 doses can also take 2 doses together; taken within 72 h of intercourse</td>
<td>• No estrogen thus very few contraindications/side effects (less nausea)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if &gt;24 h</td>
<td>• Less effective in overweight individuals (&gt;75 kg less effective, &gt;80 kg not recommended)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NON-HORMONAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcoital IUD (Copper)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Insert up to 7 d postcoitus</td>
<td>• See Table 11</td>
<td>See Table 11</td>
</tr>
<tr>
<td></td>
<td>• Prevents implantation</td>
<td>• See Table 11</td>
<td>See Table 11</td>
</tr>
<tr>
<td></td>
<td>• 1% failure rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can use for short duration in higher risk individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mirena® IUD cannot be used as EPC</td>
</tr>
</tbody>
</table>

Follow-up
- 3-4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counseling

---

**Infertility**

### Epidemiology
- 10-15% of couples
- must investigate both members of the couple

### Female Factors

**Etiology**
- ovulatory dysfunction (15-20%)
  - hypothalamic (hypothalamic amenorrhea)
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - PCOS
    - premature ovarian failure
    - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone, poorly understood
    - systemic diseases (thyroid, Cushing’s syndrome, renal/hepatic failure)
    - congenital (Turner’s syndrome, gonadal dysgenesis or gonadotropin deficiency)
    - stress, poor nutrition, excessive exercise (even with presence of menstruation)
  - outflow tract abnormality (15-20%)
    - tubal factors (20-30%)
    - PID
    - adhesions (previous surgery, peritonitis, endometriosis)
    - ligament/occlusion (e.g. previous ectopic pregnancy)
  - uterine factors (<5%)
    - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure
    - intruterine adhesions (e.g. Asherman’s syndrome)
    - infection (endometritis, pelvic TB)
    - fibroids/polyps (particularly intruterine)
    - endometrial ablation
  - cervical factors (5%)
    - hostile or acidic cervical mucus
    - anti-sperm antibodies
    - structural defects (cone biopsies, laser or cryotherapy)
- Requirements for Conception
  - Ovary
  - Tube
  - Cervix
  - Endometrium
  - Sperm

Infertility: inability to conceive or carry to term a pregnancy after 1 yr of regular, unprotected intercourse

Primary infertility: infertility in the context of no prior pregnancies

Secondary infertility: infertility in the context of a prior conception

Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr
endometriosis (15-30%)
multiple factors (30%), see GY22
unknown factors (10-15%)

Investigations
ovulatory
- day 3: FSH, LH, TSH, prolactin ± DHEA, free testosterone (if hirsute)
- day 21-23: serum progesterone to confirm ovulation
- initiate basal body temperature monitoring (biphasic pattern)
- postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
tubal factors
- HSG (can be therapeutic – opens fallopian tube)
- SHG (can be therapeutic – opens fallopian tube)
laparoscopy with dye insufflation (or tubal dye test)
peritoneal/uterine factors
- HSG/SHG, hysteroscopy
other
- karyotype

Treatment
education: timing of intercourse in relation to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
medical
- ovulation induction
  - clomiphene citrate (Clomid®): estrogen antagonist that causes a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; causes increased FSH and LH, leading to ovulation induction (works much better if anovulatory)
  - human menopausal gonadotropin – FSH and LH extracted from urine of postmenopausal women
  - followed by β-hCG for stimulation of ovum release
  - may add
    - bromocriptine (dopamine agonist) if elevated prolactin
    - dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
    - metformin (for PCOS)
    - luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
  - ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
surgical/procedural
- tubuloplasty
- lysis of adhesions
artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
sperm washing
IVF (in vitro fertilization)
IFT (intratubal transfer)
GIFT (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
ZIFT (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
TET (tubal embryo transfer): transfer after >24 h culture
ICSI (intracytoplasmic sperm injection)
IVM (in vitro maturation)
± oocyte or sperm donors
± pre-genetic screening for single gene defects in karyotype of zygote

Male Factors
see Urology, U33

Etiology
- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)

Investigations
- semen analysis and culture
- postcoital (Huhner) test: rarely done

When Should Investigations Begin?
- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo
- >40 yr: immediately
- Earlier if:
  - History of PID
  - History of infertility in previous relationship
  - Prior pelvic surgery
  - Chemotherapy/radiation in either partner
  - Recurrent pregnancy loss
  - Moderate-severe endometriosis

Controversial and Evolving Ethical Issues
Infertility demands non-judgmental discussion
Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial
If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

Normal Semen Analysis (WHO lower reference limits)
- Must be obtained after 2-7 d of abstinence
- Volume 1.5 cc
- Count 15 million/cc
- Vitality 58% live
- Motility 32% progressive, 40% total (progressive + non-progressive)
- Morphology 4.0% normal
Polycystic Ovarian Syndrome

- also called chronic ovarian androgenism

Etiology

- laboratory
  - prolactin, 17-hydroxyprogesterone, free testosterone, DHEA-S, TSH, free T₄, androstenedione, SHBG
  - LH:FSH >2:1; LH is chronically high with FSH mid-range or low (low sensitivity and specificity)
  - increased DHEA-S, androstenedione and free testosterone (most sensitive), decreased SHBG

- transvaginal or transabdominal U/S: polycystic-appearing ovaries ("string of pearls" – 12 or more small follicles 2-9 mm, or increased ovarian volume)

- tests for insulin resistance or glucose tolerance
  - fasting glucose:insulin ratio <4.5 is consistent with insulin resistance (U.S. units)
  - 75 g OGTT yearly (particularly if obese)

- laparoscopy
  - not required for diagnosis
  - most common to see white, smooth, sclerotic ovaries with a thick capsule; multiple follicular cysts in various stages of atresia; hyperplastic theca and stroma

- rule out other causes of abnormal bleeding

Treatment

- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - OCP monthly or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if type 2 diabetic or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only

- infertility
  - medical induction of ovulation: clomiphene citrate, human menopausal gonadotropins (HMG [Pergonal®]), LHRI, recombinant FSH, and metformin
  - metformin may be used alone or in conjunction with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary
  - bromocriptine (if hyperprolactinemia)

- hirsutism
  - any OCP can be used
  - Androcur® (cyproterone acetate): antiandrogenic
  - Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
  - finasteride (5-a reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone: androgen receptor inhibitor

- hyperlipidemia
- hyperprolactinemia
- hypothyroidism

Use of Metformin in Polycystic Ovary Syndrome. A Meta-Analysis

Oblast Gynecol 2008;11(4):959-68.
Study: This meta-analysis of 17 RCTs assessed the efficacy of metformin or metformin in combination with clomiphene citrate in women with PCOS who were seeking pregnancy.

Main Outcomes: Ovulation, pregnancy, and live birth. Patients: 1,639 patients with PCOS were seeking pregnancy. Results: Compared to placebo, metformin increased the odds of ovulation (OR 2.94, 95% CI 1.43-6.02). However, when used alone, metformin did not significantly increase the odds of achieving pregnancy (OR 1.58, 95% CI 0.74-3.33). When compared to clomiphene alone, the combination of metformin and clomiphene increased the likelihood of ovulation (OR 4.39, 95% CI 1.84-9.98) and pregnancy (OR 2.67, 95% CI 1.45-4.94). The effect of combination therapy was most prominent in clomiphene-resistant and obese women with PCOS. Furthermore, the combination therapy had a higher likelihood of having a live birth compared to clomiphene alone, but this did not reach significance (OR 1.74, 95% CI 0.79-3.86).

Conclusions: Metformin increases the likelihood of ovulation. When used together with clomiphene, metformin increases the likelihood of both ovulation and pregnancy, especially in clomiphene-resistant and obese women.
Gynecological Discharge

- clear, white, flocculent, odorless discharge; pH 3.8-4.2
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features
  - irritation, pruritus
  - discharge
  - vulvar erythema
  - vaginal bleeding (specifically due to Group A Streptococci and Shigella)
- differential diagnosis
  - non-specific vulvovaginitis (25-75%)
  - infections (respiratory, enteric, systemic, sexually acquired)
  - foreign body (toilet paper most common)
  - Candida (if using diapers)
  - pinworms
  - polyps, tumor (ovarian malignancy)
  - vulvar skin disease (lichen sclerosis, condyloma acuminata)
  - trauma (accidental straddle injury, sexual abuse)
  - psychosomatic vaginal complaints (specific to vaginal discharge)
  - endocrine abnormalities (specific to vaginal bleeding)
  - blood dyscrasia (specific to vaginal bleeding)
- etiology
  - infectious
    - poor hygiene, proximity of vagina to anus
    - recent infection (respiratory, enteric, systemic)
    - STD: investigate sexual abuse
  - nonspecific
    - lack of protective hair and labial fat pads
    - lack of estrogenization
    - susceptible to chemicals, soaps (bubble baths), medications, and clothing
    - enuresis
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen), pH, wet-mount, and KOH smear in adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

Table 13. Other Common Causes of Vulvovaginitis in Prepubertal Girls

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Pinworms</th>
<th>Lichen Sclerosis</th>
<th>Foreign Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Cellophane tape test</td>
<td>Area of white patches and thinning of skin</td>
<td>Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia</td>
</tr>
<tr>
<td></td>
<td>Empirical treatment with mebendazole</td>
<td>Topical steroid creams</td>
<td></td>
</tr>
</tbody>
</table>
# POSTMENOPAUSAL VAGINITIS/ATROPHIC VAGINITIS

- **Clinical Features**
  - Dyspareunia
  - Postcoital spotting
  - Mild pruritus
- **Investigations**
  - Atrophy is usually a visual diagnosis: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  - Rule out malignancy: especially endometrial cancer
- **Treatment**
  - Local estrogen replacement (ideal): Premarin® cream, VagiFem® tablets, or Estring®
  - Oral or transdermal hormone replacement therapy (if treatment for systemic symptoms is desired)
  - Good hygiene

# INFECTIOUS VULVOVAGINITIS

<table>
<thead>
<tr>
<th>Table 14. Infectious Vulvovaginitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organisms</strong></td>
</tr>
<tr>
<td>Candida albicans (90%)</td>
</tr>
<tr>
<td>Candida glabrata (≤5%)</td>
</tr>
<tr>
<td>Candida tropicalis (≤5%)</td>
</tr>
<tr>
<td><strong>Pathophysiology or Transmission</strong></td>
</tr>
<tr>
<td>Predisposing factors include:</td>
</tr>
<tr>
<td>Immunosuppressed host (DM, AIDS, etc.)</td>
</tr>
<tr>
<td>Recent antibiotic use</td>
</tr>
<tr>
<td>Increased estrogen levels (e.g. pregnancy, OCP)</td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
</tr>
<tr>
<td>Whitish, “cottage cheese,” minimal</td>
</tr>
<tr>
<td>Gray, thin, diffuse</td>
</tr>
<tr>
<td>Yellow-green, malodorous, diffuse, frothy</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>20% asymptomatic</td>
</tr>
<tr>
<td>50-75% asymptomatic</td>
</tr>
<tr>
<td>25% asymptomatic</td>
</tr>
<tr>
<td><strong>Signs/Symptoms</strong></td>
</tr>
<tr>
<td>Intense pruritus</td>
</tr>
<tr>
<td>Swollen, inflamed genitals</td>
</tr>
<tr>
<td>Vulvar burning, dysuria, dyspareunia</td>
</tr>
<tr>
<td>Fishy odor, especially after coitus</td>
</tr>
<tr>
<td>Absence of vulvar/vaginal irritation</td>
</tr>
<tr>
<td>Petechiae on vagina and cervix</td>
</tr>
<tr>
<td>Occasionally irritated tender vulva</td>
</tr>
<tr>
<td>Dysuria, frequency</td>
</tr>
<tr>
<td><strong>Ph</strong></td>
</tr>
<tr>
<td>≤4.5</td>
</tr>
<tr>
<td>≥4.5</td>
</tr>
<tr>
<td>≥4.5</td>
</tr>
<tr>
<td><strong>Saline Wetmount</strong></td>
</tr>
<tr>
<td>KOH wetmount reveals hyphae and spores</td>
</tr>
<tr>
<td>&gt;20% clue cells = squamous epithelial cells dotted with cocobacilli (Gardnerella)</td>
</tr>
<tr>
<td>Paucity of WBC</td>
</tr>
<tr>
<td>Paucity of Lactobacilli</td>
</tr>
<tr>
<td>Positive whiff test: fishy odor with addition of KOH to slide (due to formation of amines)</td>
</tr>
<tr>
<td>Motile flagellated organisms</td>
</tr>
<tr>
<td>Many WBC</td>
</tr>
<tr>
<td>Inflammatory cells (PMNs)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments</td>
</tr>
<tr>
<td>Treatment in pregnancy is usually topical</td>
</tr>
<tr>
<td>Fluconazole 150 mg PO in single dose (can be used in pregnancy)</td>
</tr>
<tr>
<td>No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure</td>
</tr>
<tr>
<td>Oral</td>
</tr>
<tr>
<td>Metronidazole 500 mg PO bid x 7 d</td>
</tr>
<tr>
<td>Topical</td>
</tr>
<tr>
<td>Metronidazole gel 0.75% x 5 d OD (may be used in pregnancy)</td>
</tr>
<tr>
<td>Clindamycin 2% 5 g intravaginally at bedtime for 7 d</td>
</tr>
<tr>
<td>Treat even if asymptomatic</td>
</tr>
<tr>
<td>Metronidazole 2 g PO single dose or 500 mg bid x 7 d (alternative)</td>
</tr>
<tr>
<td>Symptomatic pregnant women should be treated with 2 g metronidazole once</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole</td>
</tr>
<tr>
<td>Routine treatment of partner(s) not recommended (not sexually transmitted)</td>
</tr>
<tr>
<td>Associated with recurrent preterm labor, preterm birth, and postpartum endometritis</td>
</tr>
<tr>
<td>Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)</td>
</tr>
<tr>
<td>Routine treatment of partner(s) not recommended (not sexually transmitted)</td>
</tr>
<tr>
<td>Warnings accompanying metronidazole use</td>
</tr>
<tr>
<td>Treat partner(s)</td>
</tr>
</tbody>
</table>
Sexually Transmitted Diseases

- see Family Medicine, FM45

TRICHOMEONIASIS
  - see Infectious Vulvovaginitis, Table 14, GY24

CHLAMYDIA

Etiology
  - Chlamydia trachomatis

Epidemiology
  - common bacterial STD in the United States
  - often associated with N. gonorrhoeae

Clinical Features
  - asymptomatic (80% of women)
  - muco-purulent endocervical discharge
  - urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
  - pelvic pain
  - postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
  - symptomatic sexual partner

Investigations
  - cervical culture or nucleic acid amplification test
  - obligate intracellular parasite: tissue culture is the definitive standard
  - urine and vaginal tests now available, which are equally or more effective than cervical culture

Treatment
  - doxycycline 100 mg PO bid for 7 d or azithromycin 1 g PO in a single dose
  - if pregnant: azithromycin 1 g PO in a single dose or amoxicillin 500 mg PO tid for 7 d
  - also treat gonorrhea because of high rate of co-infection
  - treat partners
  - reportable disease
  - test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

Screening
  - high risk groups
  - during pregnancy
  - with initiation of OCP (independent risk factor)
Complications
- acute salpingitis, PID
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- infertility: tubal obstruction from low grade salpingitis
- ectopic pregnancy
- chronic pelvic pain
- perinatal infection: conjunctivitis, pneumonia

GONORRHEA

Etiology
- Neisseria gonorrhoeae
- symptoms and risk factors same as with chlamydia

Investigations
- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal, and throat culture (if clinically indicated)

Treatment
- single dose of ceftriaxone 250 mg IM plus single dose of azithromycin 1 g PO or doxycycline 100 mg PO bid for 7d
- if pregnant: above regimen or alternate cephalosporin, or single dose of azithromycin 2 g PO
- also treat chlamydia, because of high rate of co-infection
- treat partners
- reportable disease
- screening as with Chlamydia

HUMAN PAPILLOMAVIRUS

Etiology
- common viral STD in the United States
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

Investigations
- cytology (see Cervical Screening Pap Test, GY41)
  - koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
- patient administered
  - podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  - imiquimod (Aldara®) 5% cream 3x/wk qhs x 16 wk
  - provider administered
    - cryotherapy with liquid nitrogen: repeat q1-2wk
    - podophyllin resin 10-25% in tincture of benzoin: weekly
    - trichloroacetic acid (TCA) or bichloroacetic acid weekly (BCA) (80-90%); safe in pregnancy
    - surgical removal/laser

Prevention
- vaccination: Gardasil®, Cervarix® (see Table 24, GY43)
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)
HERPES SIMPLEX VIRUS OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: present 2-21 d following contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent and shorter in duration (especially with HSV-1)

Investigations
- viral culture preferred in patients with ulcer present, however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear)
  - multinucleated giant cells, acidophilic intranuclear inclusion bodies
- type specific serologic tests for antibodies to HSV-1 and HSV-2
- HSV DNA PCR

Treatment
- first episode
  - acyclovir 400 mg PO tid or 200 mg PO fives times daily x 7-10 d, or famciclovir 250 mg PO tid x 7-10 d, or valacyclovir 1 g PO bid x 7-10 d
- recurrent episode
  - acyclovir 400 mg PO tid or 800 mg PO bid x 5 d, or acyclovir 800 mg PO tid x 2 d; famciclovir and valacyclovir may also be used
- daily suppressive therapy
  - consider if more than 6 recurrences per yr or one every 2 mo
- acyclovir 400 mg PO bid, or famciclovir 250 mg bid, or valacyclovir 0.5-1 g PO OD
- severe disease
  - IV therapy: acyclovir 5-10 mg/kg IV q8h x 2-7 d or until clinical improvement, followed by oral antiviral therapy to complete at least 10 d
- education regarding transmission
- avoid contact from onset of prodrome until lesions have cleared
- use barrier contraception

SYPHILIS

Etiology
- *Treponema pallidum*

Classifications
- primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based fleshy gray lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

Epidemiology of Genital Ulcers
- HSV 70-80%
- 1st Syphilis 5%
- Chancroid <1%
  (Haemophilus ducreyi)
Investigations
- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis)
  - spirochetes
- non-treponemal screening tests (VDRL, RPR); nonreactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
  - treat partners, reportable disease
- treatment of latent syphilis >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
- screening
  - high risk groups
  - in pregnancy (see Obstetrics, Table 12, OB19)

Complications
- if untreated, 1/3 will experience late complications

HIV
- see Infectious Diseases, ID29

Bartholinitis/Bartholin Gland Abscess

**Etiology**
- often anaerobic and polymicrobial
- *U. urealyticum*, *N. gonorrhoeae*, *C. trachomatis*, *E. coli*, *P. mirabilis*, *Streptococcus* spp., *S. aureus* (rare)
- blockage of duct

**Clinical Features**
- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

**Treatment**
- sitz baths, warm compresses
- antibiotics: cephalexin x 1 wk
- incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
- marsupialization under general anesthetic – more definitive treatment
- rarely treated by removing gland

Pelvic Inflammatory Disease

- up to 20% of all gynecology-related hospital admissions

**Etiology**
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
  - gonorrhea and chlamydia often co-exist
  - endogenous flora: anaerobic, aerobic, or both
    - *E. coli*, *Staphylococcus*, *Streptococcus*, *Enterococcus*, *Bacteroides*, *Peptostreptococcus*, *H. influenzae*, *G. vaginalis*
  - cause of recurrent PID
  - associated with instrumentation
  - *Actinomyces israelii* (Gram-positive, non acid-fast anaerobe)
  - 1-4% of PID cases associated with IUDs
  - others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

**Risk Factors**
- age <30 yr
- risk factors as for chlamydia and gonorrhea
- vaginal douching
- IUD (within first 10 d after insertion)
- invasive gynecologic procedures (D&C, endometrial biopsy)
Clinical Presentation
- up to 2/3 asymptomatic: many subtle or mild symptoms
- common
  - fever >38.3°C
  - lower abdominal pain and tenderness
  - abnormal discharge: cervical or vaginal
- uncommon
  - N/V
  - dysuria
  - AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

Investigations
- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for N. gonorrhoeae, C. trachomatis
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

Treatment
- must treat with polymicrobial coverage
- inpatient if
  - moderate to severe illness
  - atypical infection
  - adnexal mass, tubo-ovarian or pelvic abscess
  - unable to tolerate oral antibiotics or failed oral therapy
  - immunocompromised
  - pregnant
  - adolescent – first episode
  - surgical emergency cannot be excluded (e.g. ovarian torsion)
  - PID is secondary to instrumentation
  - recommended treatment
    - cefotetan 2 g IV q12h or cefoxitin 2 g IV q6h + doxycycline 100 mg PO/IV q12h, or
    - clindamycin 900 mg IV q8h + gentamicin 2 mg/kg IV/IM loading dose followed by 1.5 mg/kg
    - loading dose q8h
  - continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO
    - bid to complete 14 d
  - percutaneous drainage of abscess under U/S guidance
  - when no response to treatment, laparoscopic drainage
  - if failure, treatment is surgical (salpingectomy, TAH/BSO)
- outpatient if
  - typical findings
  - mild to moderate illness
  - oral antibiotics tolerated
  - compliance ensured
  - follow-up within 48-72 h (to ensure symptoms not worsening)
  - recommended treatment
    - single dose cefixime 250 mg IM + doxycycline 100 mg PO bid x 14 d ± metronidazole
    - 500 mg PO bid x 14 d
    - consider removing IUD after a minimum of 24 h of treatment
    - N/V
    - reportable disease
    - treat partners
    - consider re-testing for C. trachomatis and N. gonorrhoeae 4-6 wk after treatment if
      documented infection

PID Complications
- I FACE PID
  - Infertility
  - Fitz-Hugh-Curtis syndrome
  - Abscesses
  - Chronic pelvic pain
  - Ectopic pregnancy
  - Peritonitis
  - Intestinal obstruction
  - Disseminated infection (sepsis, endocarditis, arthritis, meningitis)

PID Diagnosis
- Must have:
  - Lower abdominal pain
- Plus one of
  - Cervical motion tenderness
  - Adnexal tenderness
- Plus one or more of
  - High risk partner
  - Temperature >38°C
  - Mucopurulent cervical discharge
  - Positive culture for N. gonorrhoeae, C. trachomatis, E. coli, or other vaginal flora
  - Cul-de-sac fluid, pelvic abscess or inflammatory mass on U/S or bimanual
  - Leukocytosis
  - Elevated ESR or CRP (not commonly used)

Alternative PID Treatments
- Azithromycin (1 g PO weekly x 2 wk)
  + cefixime 250 mg IM x 1
  = metronidazole 500 mg PO bid x 14 d
- Quinolones are no longer recommended for treatment of PID due to quinolone-resistant N. gonorrhoeae

Source: Centers for Disease Control and Prevention. Sexually Transmitted Diseases Treatment Guidelines. MMWR 2010;59(RR-12):1-67
Complications of Untreated PID
- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID \(\rightarrow\) 13% infertility
  - 2 episodes of PID \(\rightarrow\) 36% infertility
- bacteremia
- septic arthritis, endocarditis

**Toxic Shock Syndrome**
- see Infectious Diseases, ID24

**Risk Factors**
- tampon use
- diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
- wound infections
- post-partum infections
- early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

**Clinical Presentation**
- sudden high fever
- sore throat, headache, diarrhea
- erythroderma
- signs of multisystem organ failure
- refractory hypotension
- exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness

**Treatment**
- remove potential sources of infection (foreign objects and wound debris)
- debride necrotic tissues
- adequate hydration
- penicillinase-resistant antibiotics, e.g. cloxacillin
- steroid use controversial but if started within 72 h, may reduce severity of symptoms and duration of fever

**Sexual Abuse**
- see Family Medicine, FM27, Emergency Medicine, ER28

**Sexual Dysfunction**

**Etiology**
- psychological or emotional: depression, abuse
- hormonal: menopause
- neurologic dysfunction: spinal cord injury
- vascular insufficiency: DM
- drug side effects: \(\beta\)-blockers
- trauma: episiotomy

**Classification**
- lack of desire (60-70% of women)
- lack of arousal
- anorgasmia (5-10%)
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but now unable to
- dyspareunia (3-6%): painful intercourse, superficial or deep
- vaginismus (15%)
- vulvodynia
- vaginal atrophy
- vulvar vestibulitis: associated with history of frequent yeast infections
- PID

**Treatment**
- lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
- anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
• dyspareunia
  - Kegel and reverse Kegel exercises
  - dilator treatment
  - comfort with self-exam
  - psychotherapy, other behavioral techniques
  - female on top position: allows for control of speed and duration
  - vestibulitis: remove local irritants, change in contraceptive methods, dietary changes (increased citrate, decreased oxalate), and vestibulotomy (rare)
  - vulvodynia: local moisturization, cold compresses, systemic nerve blocking therapy (amitriptyline, gabapentin), topical anesthetics, estrogen cream
  - pain clinic

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### Menopause

- see Family Medicine, FM42

#### Definitions
- lack of menses for 1 yr
- types of menopause
  - physiological: average age 51 yr (follicular atresia)
  - premature ovarian failure: before age 40 (autoimmune disorder, infection, Turner’s syndrome)
  - iatrogenic (surgical/radiation/chemotherapy)

#### Clinical Features
- associated with estrogen deficiency
  - vasomotor instability (tends to dissipate with time)
    - hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, palpitations
  - urogenital atrophy involving vagina, urethra, bladder
    - dyspareunia, pruritus, vaginal dryness, bleeding, urinary frequency, urgency, incontinence
  - skeletal
    - osteoporosis, joint and muscle pain, back pain
  - skin and soft tissue
    - decreased breast size, skin thinning/loss of elasticity
  - psychological
    - mood disturbance, irritability, fatigue, decreased libido, memory loss

#### Investigations
- increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
- FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
- decreased levels of estradiol (later)

#### Treatment
- goal is for individual symptom management
  - vasomotor instability
    - HRT (first line), SSRIs, venlafaxine, gabapentin, propranolol, clonidine
    - acupuncture
  - vaginal atrophy
    - local estrogen: cream (Premarin*), vaginal suppository (VagiFem*), ring (Estring*)
    - lubricants (Replens*)
  - urogenital health
    - lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery
  - osteoporosis
    - 1,000-1,500 mg calcium OD, 800-1,000 IU vitamin D, weight-bearing exercise, smoking cessation
    - bisphosphonates (e.g. alendronate)
    - selective estrogen receptor modifiers (SERMs): raloxifene (Evista*) – mimics estrogen effects on bone, avoids estrogen-like action on breast and uterine cancer; does not help hot flashes
    - HRT: second-line treatment (unless for vasomotor instability as well)
  - decreased libido
    - vaginal lubrication, counseling, androgen replacement (testosterone cream or the oral form Andro*):
      - cardiovascular disease
        - management of cardiovascular risk factors
        - mood and memory
          - antidepressants (first line), HRT (augments effect)
        - alternative choices (not evidence-based, safety not established)
          - black cohosh, phytoestrogens, St. John’s wort, gingko biloba, valerian, evening primrose oil, ginseng, Don Quai
Hormone Replacement Therapy

- see Family Medicine, FM42
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 yr)

**HRT Components**

- estrogen
  - oral or transdermal (e.g. patch, gel)
  - transdermal preferred for women with hypertriglyceridemia or impaired hepatic function, smokers, and women who suffer from headaches associated with oral HRT
  - low-dose (preferred dose: 0.3 mg Premarin®/25 µg Estradot® patch, can increase if necessary)
- progestin
  - given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

**Table 15. Examples of HRT Regimens**

<table>
<thead>
<tr>
<th>HRT Regimen</th>
<th>Estrogen Dose</th>
<th>Progestin Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed Estrogen</td>
<td>CEE 0.625 mg PO OD</td>
<td>None</td>
<td>If no intact uterus</td>
</tr>
<tr>
<td>Standard-dose</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 2.5 mg PO OD</td>
<td>Withdrawal bleeding may occur in a spotty, unpredictable manner. Usually abates after 6-8 mo due to endometrial atrophy. Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy).</td>
</tr>
<tr>
<td>Standard-dose cyclic</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 5-10 mg PO days 1-14 only, or micronized progesterone 200 mg PO OD days 1-14 only</td>
<td>Bleeding occurs monthly after day 14 of progestin (can continue for yr). PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT.</td>
</tr>
<tr>
<td>Pulsatile</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA low-dose</td>
<td>3 d on, 3 d off</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Estroderm®-Estradiol 0.05 mg/d or 0.1 mg/d Estalis®-Estradiol 140 µg/d or 250 µg/d</td>
<td>Estroderm®-MPA 2.5 mg PO OD Estalis®-NEA 50 µg/d</td>
<td>Use patch twice weekly. Can use oral progestins (Estroderm®). Combined patches available (Estalis®).</td>
</tr>
<tr>
<td>Topical</td>
<td>Estrace® 2.4 g/d x 1-2 wk, 1 g/d maintenance Premarin® 0.5-2 g/d for 21 d then off 7 d for vaginal atrophy, 0.5 g/d for 21 d then off 7 d or twice/wk for dyspareunia Estragyn® 2-4 g/d</td>
<td>Crinone® 4% or 9% (45 or 90 mg applicator)</td>
<td>If simultaneously taking oral estrogen tablet, may need to adjust dosing. If intact uterus, also take progesterone</td>
</tr>
</tbody>
</table>

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate
Consider lower dose regimen, PREMPRO® 0.45/1.5 (Premarin® 0.45 mg and Provera® 1.5 mg); Estrace® (topical 17β-estradiol) = 0.1 mg active ingredient/g; Premarin® (topical CEE) = 0.625 mg active ingredient/g; Estragyn® (topical estriol) = 1 mg active ingredient/g

**Side Effects of HRT**

- abnormal uterine bleeding
- mastodynia – breast tenderness
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

**Contraindications to HRT**

- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches

---

**Menopause Pathophysiology**

Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)

- Less estrogen is produced
- Decreased negative feedback on hypothalamic-pituitary-adrenal axis
- Increased FSH and LH
- Stromal cells continue to produce androgens as a result of increased LH stimulation

**Absolute Contraindications to HRT**

ABCD
- Acute liver disease
- Undiagnosed vaginal bleeding
- Cancer (breast/uterine), Cardiovascular disease
- DVT (thromboembolic disease)
family history of estrogen-dependent cancer  
chronic thrombophlebitis  
DM (with vascular disease)  
gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)  
fibrocystic disease of the breasts

WOMEN'S HEALTH INITIATIVE (launched in 1991)  
- two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old  
- continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus  
- estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy  
- both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE, and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm  
- the apparent increase in CHD was in disagreement with results of previous observational trial  
- results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results  
- benefits and risks reported as number of cases per 10,000 women each yr

The apparent increase in CHD was in disagreement with results of previous observational trial  
- one additional case with estrogen-alone  
- 6 fewer cases with combined HRT (WHI)  
- Colon Cancer: 8 additional cases with combined HRT, and 12 additional cases for estrogen-alone (WHI)  
- DVT/PE: 18 additional cases with combined HRT, and 9 additional cases for estrogen-alone (WHI)  
- CHD: 7 additional MIs with combined HRT (WHI); secondary analysis suggests greater absolute risk for women aged > 70 yr and for women who start HRT > 10 yr post-menopause  
- Breast Cancer: 8 additional cases with combined HRT (WHI) Risk only increased after > 5 yr of combined HRT use; no increased risk for estrogen-alone  
- Dementia and Mild Cognitive Impairment: 50% greater risk of developing dementia in women taking estrogen-alone after age 65; risk is greater for women taking combined HRT; risk of developing dementia was reduced for women taking HRT before age 65

Table 16. HRT Benefits vs. Risks

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Symptoms: less frequent and severe with use of either combined or estrogen-alone HRT</td>
<td>Stroke: 8 additional cases with combined HRT, and 12 additional cases for estrogen alone (WHI)</td>
</tr>
<tr>
<td>Osteoporosis: 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT; 6 fewer cases of hip fractures with estrogen alone</td>
<td>DVT/PE: 18 additional cases with combined HRT, and 9 additional cases for estrogen-alone (WHI)</td>
</tr>
<tr>
<td>Colon Cancer: 6 fewer cases with combined HRT (WHI) One additional case with estrogen-alone</td>
<td>CHD: 7 additional MIs with combined HRT (WHI); secondary analysis suggests greater absolute risk for women aged &gt; 70 yr and for women who start HRT &gt; 10 yr post-menopause</td>
</tr>
<tr>
<td></td>
<td>Breast Cancer: 8 additional cases with combined HRT (WHI) Risk only increased after &gt; 5 yr of combined HRT use; no increased risk for estrogen-alone</td>
</tr>
<tr>
<td></td>
<td>Dementia and Mild Cognitive Impairment: 50% greater risk of developing dementia in women taking estrogen-alone after age 65; risk is greater for women taking combined HRT; risk of developing dementia was reduced for women taking HRT before age 65</td>
</tr>
</tbody>
</table>

Urogynecology

Pelvic Relaxation/Prolapse

Etiology
- relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
- related to
  - vaginal childbirth
  - aging
  - decreased estrogen (post-menopause)
  - following pelvic surgery
  - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
  - congenital (rarely)
  - ethnicity (Caucasian women > Asian or African women)
  - collagen disorders

GENERAL CONSERVATIVE TREATMENT
(for pelvic relaxation/prolapse and urinary incontinence)
- Kegel exercises
- local vaginal estrogen therapy
- vaginal pessary (intravaginal suspension disc)
Table 17. Pelvic Prolapse

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine Prolapse</td>
<td>• Groin/back pain (stretching of uterosacral ligaments)</td>
<td>• See General Conservative Treatment, G33</td>
</tr>
<tr>
<td>(protrusion of cervix and uterus into vagina)</td>
<td>• Feeling of heaviness/pressure in the pelvis</td>
<td>• Vaginal hysterectomy ± surgical prevention of vault prolapse</td>
</tr>
<tr>
<td></td>
<td>• Worse with standing, lifting</td>
<td>• Consider additional surgical procedures if urinary incontinence, cystocele, rectocele, and/or enterocele are present</td>
</tr>
<tr>
<td></td>
<td>• Worse at the end of the day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Relieved by lying down</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Ulceration/bleeding (particularly if hypoestrogenic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± urinary incontinence</td>
<td></td>
</tr>
<tr>
<td>Vault Prolapse</td>
<td>• See General Conservative Treatment, G33</td>
<td>• Sacralcolpopexy (vaginal vault suspension), sacrospinous fixation, or uterosacral ligament suspension</td>
</tr>
<tr>
<td>(protrusion of apex of vaginal vault into vagina, post-hysterectomy)</td>
<td>• Frequency, urgency, nocturia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Stress incontinence</td>
<td>• See General Conservative Treatment, G33</td>
</tr>
<tr>
<td></td>
<td>• Incomplete bladder emptying ± associated increased incidence of urinary tract infections – may lead to renal impairment</td>
<td>• Consider additional/alternative surgical procedure if documented urinary stress incontinence</td>
</tr>
<tr>
<td>Cystocele</td>
<td>• Straining/digitation to evacuate stool</td>
<td>• See General Conservative Treatment, G33</td>
</tr>
<tr>
<td>(protrusion of bladder into the anterior vaginal wall)</td>
<td>• Constipation</td>
<td>• Anterior colporrhaphy (“anterior repair”)</td>
</tr>
<tr>
<td>Rectocele</td>
<td>• Similar to hernia repair</td>
<td>• Also laxatives and stool softeners</td>
</tr>
<tr>
<td>(protrusion of rectum into posterior vaginal wall)</td>
<td>• Contents reduced, neck of perineal sac ligated, uterosacral ligaments, and levator ani muscles approximated</td>
<td>• Posterior colporrhaphy (&quot;posterior repair&quot;), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)</td>
</tr>
<tr>
<td>Enterocele</td>
<td>• Similar to hernia repair</td>
<td></td>
</tr>
<tr>
<td>(protrusion of small bowel in upper posterior vaginal wall)</td>
<td>• Contents reduced, neck of perineal sac ligated, uterosacral ligaments, and levator ani muscles approximated</td>
<td></td>
</tr>
</tbody>
</table>

Urinary Incontinence

- see Urology, U5

STRESS INCONTINENCE

Definition
- involuntary loss of urine with increased intra-abdominal pressure (coughing, laughing, sneezing, walking, running)
Risk Factors for Stress Incontinence in Women
• pelvic prolapse
• pelvic surgery
• vaginal delivery
• hypoestrogenic state (post-menopause)
• age
• smoking
• neurological/pulmonary disease

Treatment
• see General Conservative Treatment, GY33
• surgical
  ▪ tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

URGE INCONTINENCE

Definition
• urine loss associated with an abrupt, sudden urge to void
• “overactive bladder”
• diagnosed based on symptoms

Etiology
• idiopathic (90%)
• detrusor muscle overactivity (“detrusor instability”)

Associated Symptoms
• frequency, urgency, nocturia, leakage

Treatment
• behavior modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
• Kegel exercises
• medications
  ▪ anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  ▪ tricyclic antidepressants: imipramine

ENDOMETRIAL CARCINOMA

Epidemiology
• most common gynecological malignancy in North America (40%); 4th most common cancer in women
• 2-3% of women develop endometrial carcinoma during lifetime
• mean age is 60 yr
• majority are diagnosed in early stage due to detection of symptoms
• 85-90% 5 yr survival for stage I disease
• 70-80% overall 5 yr survival for all stages

Risk Factors
• Type I: excess estrogen (estrogen unopposed by progesterone)
  ▪ obesity
  ▪ PCOS
  ▪ unbalanced HRT (balanced HRT is protective)
  ▪ nulliparity
  ▪ late menopause
  ▪ estrogen-producing ovarian tumors (e.g. granulosa cell tumors)
  ▪ HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome
  ▪ tamoxifen
• Type II: not estrogen-related
  ▪ possibly tamoxifen

Classification and Clinical Features
• Type I (well-differentiated endometrioid adenocarcinoma) ~80% of cases:
  ▪ postmenopausal bleeding in majority, abnormal uterine bleeding in majority of affected pre-menopausal women (menorrhagia, intermenstrual bleeding)
• Type II (serous, clear cell carcinoma, grade 3 endometrioid, undifferentiated, carcinosarcoma) ~15% of cases:
  ▪ may not present with bleeding in early stage, more likely to present with advanced stage disease with symptoms like ovarian cancer (i.e. bloating, bowel dysfunction, pelvic pressure)

Investigations
• endometrial sampling
  ▪ office endometrial biopsy
  ▪ D&C ± hysteroscopy
• ± pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
  ▪ not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

Table 18. FIGO Staging of Endometrial Cancer (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to corpus</td>
<td>IB</td>
<td>Invades through ≥ ½ of myometrium</td>
</tr>
<tr>
<td>IA</td>
<td>No or less than half myometrial invasion</td>
<td>IB1</td>
<td>Positive pelvic LN</td>
</tr>
<tr>
<td>IB</td>
<td>Invades through ≥ ½ of myometrium</td>
<td>IB2</td>
<td>Positive para-aortic LN ± positive pelvic LN</td>
</tr>
<tr>
<td>II</td>
<td>Tumor invades cervical stroma, but does not extend beyond uterus*</td>
<td>II1</td>
<td>Invasion of bladder ± bowel mucosa ± distant metastases</td>
</tr>
<tr>
<td>IIIA</td>
<td>Local and/or regional spread of the tumor</td>
<td>II1A</td>
<td>Invasion of bladder ± bowel mucosa</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal ± parametral involvement</td>
<td>II1B</td>
<td>Distant mets, including intra-abdominal mets ± inguinal LNs</td>
</tr>
</tbody>
</table>

FIGO: International Federation of Gynecology and Obstetrics
*Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

Spread
• direct extension is most common
• lymphatic spread to pelvic and para-aortic nodes
• transtubal dissemination to peritoneal cavity
• hematogenous spread (usually to lungs, liver)

Treatment
• surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
  ▪ goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
  ▪ laparoscopic approach associated with improved quality of life (optimal for most patients)
• adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
• chemotherapy: often used for recurrent disease (especially if high grade or aggressive histology)
• hormonal therapy: progestins can be used for recurrent disease (especially if low grade)

UTERINE SARCOMA
• rare; 2-6% of all uterine malignancies
• arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
• behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5 yr survival is 35%
• vaginal bleeding is most common presenting symptom

Risk Factors for Endometrial Cancer
COLD NUT
Cancer (ovarian, breast, colon)
Obesity
Late menopause
DM
Nulliparity
Unopposed estrogen: PCOS, anovulation, HRT
tamoxifen: chronic use

Postmenopausal bleeding = endometrial cancer until proven otherwise (95% present with vaginal bleeding)

An endometrial thickness of 5 mm or more is considered abnormal in a postmenopausal woman with vaginal bleeding

True Pelvis
Area of pelvis between pelvic inlet and outlet, i.e. it does not include the abdominal contents in the pelvis found above the pelvic inlet

Prognostic Factors
Most important is FIGO stage
Other Prognostic Factors:
• Age
• Grade
• Histologic subtype
• Depth of myometrial invasion
• Presence of lymphovascular space involvement (LVSI)
• Hormone receptor status

Uterine Sarcoma – Symptoms
BAD-P
Bleeding
Abdominal distention
Foul smelling vaginal Discharge
Pelvic Pressure
Table 19. Summary of Uterine Sarcoma Subtypes and Features

<table>
<thead>
<tr>
<th>Type</th>
<th>Epidemiology</th>
<th>Features</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PURE TYPE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Leiomyosarcoma</td>
<td>• Accounts for 40%</td>
<td>• Histologic distinction from leiomyoma</td>
<td>• Often post-operatively after uterus removed for presumed fibroids</td>
<td>• Hysterectomy/BSO usually</td>
</tr>
<tr>
<td></td>
<td>• Average age of presentation is 55 yr but may present in pre-menopause</td>
<td>1. Increased mitotic count (&gt; 10 mitoses/10 high power fields)</td>
<td>• Staging using FIGO 2009 staging for leiomyosarcomas</td>
<td>• No routine pelvic lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td>• Often coexists with benign leiomyomata (fibroids)</td>
<td>2. Tumor necrosis</td>
<td></td>
<td>• Adjuvant chemotherapy may be used if tumor has spread beyond uterus, for palliation</td>
</tr>
<tr>
<td></td>
<td>• 50% arise within a fibroid (&quot;sarcomatous degeneration&quot;)</td>
<td>3. Cellular atypia</td>
<td></td>
<td>• Radiation therapy does not improve local control or survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Rapidly enlarging fibroids in a pre-menopausal woman</td>
<td></td>
<td>• Poor outcomes overall, even for early stage disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Enlarging fibroids in a postmenopausal woman</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Endometrial Stromal Sarcoma (ESS)</td>
<td>• Accounts for 10-15%</td>
<td>• Abnormal uterine bleeding</td>
<td>• Diagnosed by histology of endometrial biopsy or DBc</td>
<td>• Hysterectomy/BSO (remove ovaries as ovarian hormones may stimulate growth)</td>
</tr>
<tr>
<td></td>
<td>• Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding</td>
<td>• Good prognosis</td>
<td></td>
<td>• No routine pelvic lymphadenectomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Adjuvant therapy based on stage and histologic features (hormones and/or radiation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Hormonal therapy (progestins) may be used for metastatic disease</td>
</tr>
<tr>
<td>3. Undifferentiated Sarcoma</td>
<td>• Accounts for 5-10%</td>
<td>• Severe nuclear pleomorphism, high mitotic activity, tumor cell necrosis, and lack smooth muscle or endometrial stromal differentiation</td>
<td>• Often found incidentally post-operatively for abnormal bleeding</td>
<td>• Treatment primarily surgical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Poor prognosis</td>
<td></td>
<td>• Radiation and/or chemotherapy for advanced diseased or unresectable disease</td>
</tr>
<tr>
<td><strong>MIXED TYPE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Adenosarcoma</td>
<td>• The rarest of the uterine sarcoma</td>
<td>• Present with abnormal vaginal bleeding</td>
<td>• Mixture of benign epithelium with malignant low-grade sarcoma</td>
<td>• Treatment is surgical with TAH/BSO</td>
</tr>
<tr>
<td></td>
<td>• Mixed tumor of low malignant potential</td>
<td>• Polypoid mass in uterine cavity</td>
<td>• Often found incidentally at time of hysterectomy for PMB</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RECLASSIFIED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Carcinosarcoma</td>
<td>• Most common (43%)</td>
<td>• Both epithelial and stromal malignant elements present</td>
<td>• Diagnosed by histology of endometrial biopsy or DBc</td>
<td>• Usually treated as &quot;high grade endometrial carcinoma&quot; since behavior and treatment similar (i.e. surgical staging and resection of any gross metastatic disease, adjuvant chemotherapy and radiation)</td>
</tr>
<tr>
<td></td>
<td>• Recently reclassified as high grade endometrioid carcinoma with associated metaplasia of the mesenchyme, rather than arising separately from stroma</td>
<td>• Tend to form bulky polyloid masses that often fill uterine cavity and extend into or through the endocervical canal – often have extrauterine disease at presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Surgical staging using FIGO 2009 staging for endometrial cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 20. FIGO Staging of Uterine Sarcoma (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
<td>III</td>
<td>Tumor invades abdominal tissues, one site</td>
</tr>
<tr>
<td>IIA</td>
<td>&lt; 5 cm</td>
<td>IIA</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IIIB</td>
<td>&gt; 5 cm</td>
<td>IIIC</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends beyond uterus</td>
<td>IV</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IIA</td>
<td>To the pelvis, adnexal involvement</td>
<td>IVA</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>IIB</td>
<td>To extra-uterine pelvic tissue</td>
<td>IVB</td>
<td></td>
</tr>
</tbody>
</table>

Ovary

**BENIGN OVARIAN TUMORS**
- see Table 21
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumor – rare

**Ovarian Tumor Markers**
- Epithelial cell – CA-125
- Stromal
  - Granulosa cell – inhibin
  - Sertoli-Leydig – androgens
- Germ cell
  - Dysgerminoma – LDH
  - Yolk sac – AFP
- Choriocarcinoma – β-hCG
- Immature Teratoma – none
- Embryonal cell – AFP + β-hCG
MALIGNANT OVARIAN TUMORS
• see Table 21

Epidemiology
• lifetime risk 1.4% (1/70)
• in women >50 yr, more than 50% of ovarian tumors are malignant
• causes more deaths in North America than all other gynecologic malignancies combined
• 4th leading cause of cancer death in women
• 65% epithelial; 35% non-epithelial
• 5-10% of epithelial ovarian cancers are related to hereditary predisposition

Risk Factors (for epithelial ovarian cancers)
• excess estrogen
  ▪ nulliparity
  ▪ early menarche/late menopause
• age
• family history of breast, colon, endometrial, ovarian cancer
• race: Caucasian

Protective Factors (for epithelial ovarian cancers)
• OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
• pregnancy/breastfeeding
• tubal ligation (recently questioned)
• hysterectomy (without removal of ovaries)
• BSO (prophylactic surgery performed for this reason in high risk women – i.e. BRCA mutation carriers)

Screening
• no effective method of mass screening
• routine CA-125 level measurements or U/S not recommended
  ▪ high false positive rates
• controversial in high risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
  ▪ familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
  ▪ other cancers (e.g. endometrial, breast, colon)
• BRCA-1 or BRCA-2 mutation: may recommend prophylactic bilateral oophorectomy after age 35 or when child-bearing is completed

Clinical Features
• most women with epithelial ovarian cancer present with advanced stage disease since often “asymptomatic” until disseminated disease (symptoms with early stage disease are vague and non-specific)
• when present, symptoms may include
  ▪ abdominal symptoms (nausea, bloating, dyspepsia, anorexia, early satiety)
  ▪ symptoms of mass effect
    ✤ increased abdominal girth – from ascites or tumor itself
    ✤ urinary frequency
    ✤ constipation
  ▪ postmenopausal bleeding; irregular menses if pre-menopausal (rare)

Low Malignant Potential (also called “Borderline”) Tumors
• pregnancy, OCP, and breastfeeding are protective factors
• ~15% of all epithelial ovarian tumors
• tumor cells display malignant characteristics histologically, but no invasion is identified
• able to metastasize, but not commonly
• treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
  ▪ NO proven benefit of chemotherapy
• generally slow growing, excellent prognosis
  ▪ 5 yr survival >99%
• recurrences tend to occur late, may be associated with low grade serous carcinoma
<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNCTIONAL TUMORS (all benign)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular Cyst</td>
<td>Follicle fails to rupture during ovulation</td>
<td>Usually asymptomatic</td>
<td>4-8 cm mass, unilocular, lined with granulosa cells</td>
<td>Symptomatic or suspicious masses warrant surgical exploration Otherwise if &lt;6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle OCP (ovarian suppression) – will prevent development of new cysts Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice)</td>
</tr>
<tr>
<td>Lutein Cyst</td>
<td>Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic</td>
<td>More likely to cause pain than follicular cyst</td>
<td>Larger (10-15 cm) and firmer than follicular cysts</td>
<td>Same as for follicular cysts</td>
</tr>
<tr>
<td>Theca-Lutein Cyst</td>
<td>Due to atretic follicles stimulated by abnormal β-hCG levels</td>
<td>Associated with molar pregnancy, ovulation induction with clomiphene</td>
<td></td>
<td>Conservative Cyst will regress as β-hCG levels fall</td>
</tr>
<tr>
<td>Endometrioma</td>
<td>See <em>Endometriosis</em>, GY13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic Ovaries</td>
<td>See <em>PCOS</em>, GY22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BENIGN GERM-CELL TUMORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign Cystic Teratoma (dermoid)</td>
<td>Single most common ovarian germ cell neoplasm</td>
<td>May rupture, twist, infarct</td>
<td>Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic</td>
<td>Treatment usually laparoscopic cystectomy; may recur</td>
</tr>
<tr>
<td><strong>MALIGNANT GERM-CELL TUMORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Rapidly growing, 2-3% of all ovarian cancers</td>
<td>Usually children and young women (&lt;30 yr)</td>
<td></td>
<td>Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy</td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>Produces LDH</td>
<td>10% bilateral</td>
<td></td>
<td>Usually very responsive to chemotherapy, therefore complete resection is not necessary for cure</td>
</tr>
<tr>
<td>Immature Teratoma</td>
<td>No tumor marker identified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gonadoblastoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPITHELIAL OVARIAN TUMORS (malignant or borderline)</strong></td>
<td>Derived from mesothelial cells lining peritoneal cavity</td>
<td>Varies depending on subtype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>Most common ovarian tumor 50% of all ovarian cancers</td>
<td>20-30% bilateral</td>
<td>Lining similar to fallopian tube epithelium Often multicellular Histologically contain Psammoma bodies (calcified concentric concretions)</td>
<td></td>
</tr>
</tbody>
</table>

*Note: β-hCG = human chorionic gonadotropin, LDH = lactate dehydrogenase, BSO = bilateral salpingo-oophorectomy, IV = intravenous, BSO = bilateral salpingo-oophorectomy.*
Table 21. Ovarian Tumors (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPITHELIAL OVARIAN TUMORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mucinous</td>
<td>20% of epithelial tumors</td>
<td>Rarely</td>
<td>Poor response to</td>
<td>chemotherapy</td>
</tr>
<tr>
<td></td>
<td>85% benign</td>
<td>complicated</td>
<td>chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>by Pseudomyxoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>peritonei:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td>implants seed</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>abdominal</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>cavity and</td>
<td></td>
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<td></td>
<td></td>
<td>produce large</td>
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<tr>
<td></td>
<td></td>
<td>quantities of</td>
<td></td>
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<td></td>
<td></td>
<td>mucin</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Resembles</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>endocervical</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>epithelium</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Often multilocular</td>
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<td></td>
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<td></td>
<td></td>
<td>May reach</td>
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<td></td>
<td></td>
<td>enormous size</td>
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<td></td>
</tr>
<tr>
<td>SEX CORD STROMAL OVARIAN</td>
<td></td>
<td></td>
<td>Surgical resection</td>
<td>..................................................................</td>
</tr>
<tr>
<td>TUMORS</td>
<td></td>
<td></td>
<td>of tumor</td>
<td>..................................................................</td>
</tr>
<tr>
<td>Fibroma/Thecoma (benign)</td>
<td>From mature fibroblasts in ovarian stroma</td>
<td>Non-functioning</td>
<td>Firm, smooth</td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasionally</td>
<td>rounded tumor with</td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>associated</td>
<td>interlacing</td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with Meig’s</td>
<td>fibrocytes</td>
<td>..................................................................</td>
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<tr>
<td></td>
<td></td>
<td>syndrome (e</td>
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<td>..................................................................</td>
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<tr>
<td></td>
<td></td>
<td>nigmatic</td>
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<td>..................................................................</td>
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<tr>
<td></td>
<td></td>
<td>epithelial</td>
<td></td>
<td>..................................................................</td>
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<tr>
<td></td>
<td></td>
<td>tumor and</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ascites or</td>
<td></td>
<td>..................................................................</td>
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<tr>
<td></td>
<td></td>
<td>positive</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>peritoneal</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>washings</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td>Sertoli-Leydig Cell Tumor</td>
<td>Can measure elevated androgens as tumor markers</td>
<td>Androgen-producing</td>
<td>Histologic hallmark</td>
<td>..................................................................</td>
</tr>
<tr>
<td>(benign or malignant)</td>
<td></td>
<td>→ virilizing</td>
<td>of cancer</td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>effects</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(hirsutism,</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>deep voice,</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>recession of</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td></td>
<td></td>
<td>front hairline</td>
<td></td>
<td>..................................................................</td>
</tr>
<tr>
<td>METASTATIC OVARIAN TUMORS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From GI Tract,</td>
<td>4-8% of ovarian malignancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast,</td>
<td>Kronenberg tumor – metastatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endometrium,</td>
<td>ovarian tumor (usually GI tract,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>commonly stomach or colon, breast)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>with “signet-ring” cells</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
  - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynecologic oncology referral (see sidebar)
  - blood work: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
  - radiology
    - bone scan or PET scan not indicated
    - transvaginal ultrasound best to visualize ovaries
    - CT scan abdomen and pelvis to look for metastatic disease
  - try to rule out other primary source if suspected, based on:
    - occult blood per rectum: endoscopy ± barium enema
    - gastric symptoms, gastroscopy ± upper GI series
    - abnormal vaginal bleeding, endometrial biopsy to rule out concurrent endometrial cancer, colposcopy ± ECC to rule out cervical cancer if abnormal cervix
    - breast lesion identified or risk factors present: mammogram

Table 22. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Growth limited to the ovaries</td>
</tr>
<tr>
<td>IA</td>
<td>1 ovary, no ascites, no tumor on external surface, capsule intact</td>
</tr>
<tr>
<td>IB</td>
<td>2 ovaries, no ascites, no tumor on external surface, capsule intact</td>
</tr>
<tr>
<td>IC</td>
<td>1 or 2 ovaries with any of the following: capsule ruptured, tumor on ovarian surface, or malignant cells in ascites</td>
</tr>
<tr>
<td>II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension ± metastases to uterus/tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic structures</td>
</tr>
<tr>
<td>IIC</td>
<td>IIA/B with malignant cells in ascites or positive peritoneal washings</td>
</tr>
<tr>
<td>III</td>
<td>Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes; superficial liver mets is Stage III</td>
</tr>
<tr>
<td>IIIA</td>
<td>Microscopic peritoneal metastasis beyond pelvis, LNs negative</td>
</tr>
<tr>
<td>IIIB</td>
<td>Macroscopic peritoneal metastasis beyond pelvis &lt; 2 cm, LNs negative</td>
</tr>
<tr>
<td>IIIC</td>
<td>Implant &gt; 2 cm and/or retroperitoneal or inguinal nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis beyond peritoneal cavity</td>
</tr>
</tbody>
</table>

FIGO = International Federation of Gynecology and Obstetrics
Cervix

BENIGN CERVICAL LESIONS

- Nabothian cyst/inclusion cyst
  - no treatment required
- endocervical polyps
  - treatment is polypectomy (office procedure)

MALIGNANT CERVICAL LESIONS

Epidemiology
- majority are SCCs (95%); adenocarcinomas increasing (5%); rare subtypes include SCC, adenosquamous
- 8,000 deaths annually in North America
- annual Pap test reduces a woman’s chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

Etiology
- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from squamous to columnar)
  - a new squamocolumnar junction forms as a result
- the transformation zone (TZ ) is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
- dysplasia → carcinoma in situ (CIS) → invasion
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

Risk Factors
- HPV infection
  - see Sexually Transmitted Diseases, GY26
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
- high risk behaviors (risk factors for HPV infection)
  - multiple partners
  - other STDs (HSV, trichomonas)
  - early age at first intercourse
  - high risk male partner
  - smoking
- at-risk groups include:
  - sex-trade workers
  - low socioeconomic status

Cervical Cancer Screening Guidelines (Pap Test)
- see Family Medicine, FM5

Clinical Features
- SCC: exophytic, fungating tumor
- adenocarcinoma: endophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - postcoital bleeding
- late
  - 80-90% present with bleeding: either postcoital, postmenopausal or irregular bleeding
  - pelvic or back pain (extension of tumor to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix

Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions
  - U = 1 (for U/S scores of 0 or 1)
  - U = 4 (for U/S scores of 2-5)

Menopausal Status
- Postmenopausal: M = 4
- Premenopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI >200: Gynecologic oncology referral is recommended

A Risk of Malignancy Incorporating CA125, Ultrasound, and Menopausal Status for the Accurate Pre-Operative Diagnosis of Ovarian Cancer

RMI = U x M x CA-125

Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions
  - U = 1 (for U/S scores of 0 or 1)
  - U = 4 (for U/S scores of 2-5)

Menopausal Status
- Postmenopausal: M = 4
- Premenopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI >200: Gynecologic oncology referral is recommended

Figure 17. The cervix

Original squamous epithelium
Squamous metaplasia
- Columnar epithelium

Gland opening

External os

Original squamo-columnar junction

New squamo-columnar junction

© Ayalah Hutchins

CA-125 is indicated for monitoring response to treatment

Malignant Ovarian Tumor Prognosis

5 yr Survival
- Stage I: 75-95%
- Stage II: 60-75%
- Stage III: 23-41%
- Stage IV: 11%

Causes of Elevated CA-125
- Age influences reliability of test as a tumor marker
- 50% sensitivity in early stage ovarian cancer (poor) — therefore not good for screening

Malignant
- Gyne: ovary, uterus
- Non-Gyne: pancreas, stomach, colon, rectum

Non-Malignant
- Gyne: benign ovarian neoplasm, endometriosis, pregnancy, fibroids, PID
- Non-Gyne: cirrhosis, pancreatitis, renal failure

Figure 17. The cervix

© Ayalah Hutchins
Diagnosis

- apply acetic acid and identify acetowhite lesions, punctuation, mosaicism, and abnormal blood vessels to guide cervical biopsy
- endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
- diagnostic excision (LEEP) if lesion extends into endocervical canal
  - positive ECC
  - discrepancy between Pap test results and colposcopy
  - microinvasive carcinoma
- consider cold knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including EUA), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, IVP, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

Treatment: Prevention and Management

Prevention: HPV Vaccine

- two vaccines currently approved (Gardasil®, Cervarix®)

Table 23. Comparison of Two Vaccines against Human Papillomavirus (HPV)

<table>
<thead>
<tr>
<th></th>
<th>Gardasil®</th>
<th>Cervarix®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral strains covered</td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td>Route of administration</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>Schedule of dosing</td>
<td>0, 2, 6 mo</td>
<td>0, 1, 6 mo</td>
</tr>
<tr>
<td>Side effects</td>
<td>Local: redness, pain, swelling General: headache, low grade fever, GI upset</td>
<td>Local: redness, pain, swelling General: headache, low grade fever, GI upset</td>
</tr>
<tr>
<td>Approved age</td>
<td>Females age 9-45, males age 9-25</td>
<td>Females age 10-25</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnant women and women who are nursing (limited data)</td>
<td></td>
</tr>
</tbody>
</table>

- should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
- may be given at the same time as hepatitis B or other vaccines using a different injection site
- not for treatment of active infections
- most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
- conception should be avoided until 30 d after last dose of vaccination

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure; cervical intraepithelial neoplasia (CIN) or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy.

Efficacy of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine Against Cervical Infection and Precancer Caused by Oncogenic HPV Types (PATRICIA): Final Analysis of a Double-Blind, Randomized Study in Young Women

Lancet 2009;374:301-314

Study: Phase III double-blind, controlled RCT.

Patients: 18,644 women aged 15-25.

Selected Outcomes: Development of HPV-16/18 associated CIN II+ was the primary outcome. Secondary to this were persistence of infections with HPV-16, HPV-18, or other oncogenic HPV types.

Selected Results: Efficacy against development of HPV-16/18 associated CIN II+ was 98.1% (p<0.0001). High levels of cross-protection were observed for persistent infection with HPV-31 and HPV-45 and HPV-31 or HPV-45 associated CIN II+.

Conclusions: The HPV-16/18 AS04-adjuvanted vaccine protected against HPV-16/18 associated CIN II+ lesions and lesions associated with HPV-31, HPV-33, and HPV-45.
Table 24. Management of Patients Abnormal Cervical Histology and Cervical Cancer

<table>
<thead>
<tr>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN I</td>
</tr>
<tr>
<td>• Preferred option for biopsy-proven CIN I is observation</td>
</tr>
<tr>
<td>• Repeat assessment and cytology in 12 mo</td>
</tr>
<tr>
<td>• Management according to cytology results</td>
</tr>
<tr>
<td>If after HSIL or AGC</td>
</tr>
<tr>
<td>• Cytology and histology should be reviewed</td>
</tr>
<tr>
<td>• If discrepancy remains, excisional biopsy may be considered</td>
</tr>
<tr>
<td>CIN II and CIN III</td>
</tr>
<tr>
<td>Women ≥25 yr</td>
</tr>
<tr>
<td>• CIN II or III should be treated</td>
</tr>
<tr>
<td>• Excisional procedures preferred for CIN III</td>
</tr>
<tr>
<td>• Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage</td>
</tr>
<tr>
<td>• Treatment for recurrent CIN II or III should be by excision</td>
</tr>
<tr>
<td>Women &lt;25 yr</td>
</tr>
<tr>
<td>• Pathologist should be asked to clarify whether lesion is CIN II or CIN III</td>
</tr>
<tr>
<td>• CIN II: observe with colposcopy at 6-mo intervals for up to 24 mo before treatment considered</td>
</tr>
<tr>
<td>• CIN III: should be treated</td>
</tr>
<tr>
<td>During pregnancy:</td>
</tr>
<tr>
<td>• CIN II or III suspected or diagnosed during pregnancy, repeat colposcopy and treatment delayed until 8-12 wk after delivery</td>
</tr>
<tr>
<td>Stage IA1 (no LVSI)</td>
</tr>
<tr>
<td>• Trachelectomy (removal of only the cervix) if future fertility desired (and lesion ≤2 cm)</td>
</tr>
<tr>
<td>• Simple hysterectomy if future fertility is not desired</td>
</tr>
<tr>
<td>Stage IA2, IB1</td>
</tr>
<tr>
<td>• Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study)</td>
</tr>
<tr>
<td>• Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy</td>
</tr>
<tr>
<td>• Advantage is that ovaries can be spared if pre-menopausal</td>
</tr>
<tr>
<td>• For fertility preservation, may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease</td>
</tr>
<tr>
<td>• Concurrent chemoradiation therapy if adverse high risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins</td>
</tr>
<tr>
<td>Stages IB2 (&gt;4 cm), II, III, IV</td>
</tr>
<tr>
<td>• Primary chemoradiation therapy</td>
</tr>
<tr>
<td>• PET/CT to grade: evaluate pelvic and para-aortic nodes</td>
</tr>
<tr>
<td>• For positive nodes on PET: primary chemoradiation with extended field RT</td>
</tr>
<tr>
<td>• Hysterectomy generally not suggested following primary treatment with curative intent</td>
</tr>
</tbody>
</table>

Abnormal Pap Tests in Pregnancy
- incidence: 1/2,200
- Pap test at all initial prenatal visits
  - if abnormal Pap or suspicious lesion, refer to colposcopy
- if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
- if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
- if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
  - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
  - recommendations in T2/T3: delay of therapy until viable fetus and C/S for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium
- biopsy is necessary to make diagnosis and/or rule out malignancy
- hyperplastic dystrophy (squamous cell hyperplasia)
  - surface thickened and hyperkeratotic
  - pruritus most common symptom
- typically postmenopausal women
- treatment: 1% fluorinated corticosteroid ointment bid for 6 wk

CDC Advisory Committee on Immunization Practices (ACIP) Recommends Quadrivalent HPV4 Vaccine for Males
- Routine HPV4 vaccination for males aged 11-12 as a 3-dose series
- HPV4 vaccination for males aged 13-21 who have not been vaccinated previously or have not completed the 3-dose series
- Males 22-26 yr of age may be vaccinated

Source: Centers for Disease Control and Prevention. Recommendations on the Use of Quadrivalent Human Papillomavirus Vaccine in Males – Advisory Committee on Immunization Practices (ACIP), 2011. MMWR 2011;60:1705-1708

Cervical Cancer Prognosis
5 yr Survival
- Stage 0 99%
- Stage I 75%
- Stage II 55%
- Stage III 30%
- Stage IV 7%
- Overall 50-60%

Cervical cancer is most prevalent in developing countries and therefore is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies, such as CT and MRI

Cervical Cancer Prognosis

5 yr Survival
- Stage 0 99%
- Stage I 75%
- Stage II 55%
- Stage III 30%
- Stage IV 7%
- Overall 50-60%

Any suspicious lesion of the vulva should be biopsied
• lichen sclerosis
  - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
  - pruritus, dyspareunia, burning
  - figure of 8’ distribution
  - most common in postmenopausal women but can occur at any age
  - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down
  - mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
    - hyperkeratotic areas with areas of thin, shiny epithelium
    - treatment: fluorinated corticosteroid ointment

Tumors
• papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNANT VULVAR LESIONS

Epidemiology
• 5% of genital tract malignancies
• 90% SCC; remainder melanomas, basal cell carcinoma, Paget’s disease, Bartholin’s gland carcinoma
  - Type I disease: HPV-related (50-70%)
    - more likely in younger women
    - 90% of VIN contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    - usually postmenopausal women

Risk Factors
• HPV infection
• VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  - progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cautery) vs. local immunotherapy (imiquimod)

Clinical Features
• many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
• most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
• localized pruritus or lesion most common
• less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
• patterns of spread
  - local
  - groin lymph nodes (usually inguinal → pelvic nodes)
  - hematogenous

Investigations
• ± colposcopy
• ALWAYS biopsy any suspicious lesion

Prognosis
• depends on stage – particularly nodal involvement (single most important predictor followed by tumor size)
• lesions >4 cm associated with poorer prognosis
• overall 5 yr survival rate: 79%

Fallopian Tube

• least common site for carcinoma of female reproductive system (0.3%)
• usually serous epithelial carcinoma
• recently considered to be origin of serous ovarian cancer
• more common in fifth and sixth decade

Clinical Features
• classic triad present in minority of cases, but very specific
  - watery discharge (most specific) = “hydrops tubae profluens”
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain
• most patients present with a pelvic mass (see Ovarian Cancer, GY37 for guidelines regarding diagnosis/investigation)

Treatment
• as for malignant epithelial ovarian tumours
Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast

Epidemiology
- 1/1,000 pregnancies
- marked geographic variation – as high as 1/125 in Taiwan
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

HYDATIDIFORM MOLE (Benign GTD)

Complete Mole
- most common type of hydatidiform mole
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues, or membranes present
- 46XX or 46XY; chromosomes completely of paternal origin (90%)
- 2 sperm fertilize empty egg or 1 sperm with reduplication
- 15-20% risk of progression to malignant sequelae
- risk factors:
  - geographic (South East Asia most common)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency) – not proven
- clinical features:
  - often present during apparent pregnancy with abnormal symptoms/findings:
    - vaginal bleeding (97%)
    - excessive uterine size for LMP (51%)
    - theca-lutein cysts >6 cm (50%)
    - preeclampsia (27%)
    - hyperemesis gravidarum (26%)
    - hyperthyroidism (7%)
    - β-hCG >100,000 IU/L
    - β-hCG >100,000 IU/L
    - no fetal heart beat detected

Partial (or Incomplete) Mole
- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXY, XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
  - low risk of progression to malignant sequelae (<4%)
  - associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations
- clinical features:
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

Investigations
- quantitative β-hCG levels (tumor marker) abnormally high for gestational age
- U/S findings:
  - if complete: no fetus (classic "snow storm" due to swelling of villi)
  - if partial: molar degeneration of placenta ± fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation:
  - local uterine invasion as high as 31%
  - β-hCG >100,000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts

Treatment
- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- consider hysterectomy (if patient no longer desires fertility)
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

Follow-up
- contraception required to avoid pregnancy during entire follow-up period
- serial β-hCGs (as tumor marker) every wk until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of β-hCG indicates GTN → patient needs chemotherapy

GTN Diagnosis
- β-hCG plateau: <10% drop in β-hCG over four values in 3 wk (e.g. days 1, 7, 14, and 21) OR
- β-hCG rise >20% in any two values over two wk or longer (e.g. measure at days 1, 7, 14) OR
- β-hCG persistently elevated >6 mo OR
- Metastases on workup
**GTN (MALIGNANT GTD)**

**Invasive Mole or Persistent GTN**
- diagnosis made by rising or plateau in β-hCG, development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

**Choriocarcinoma**
- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no chorionic villi, elements of syncytiotrophoblast, and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

**Placental-site Trophoblastic Tumor**
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low β-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

**CLASSIFICATION of GTN**
- non-metastatic
  - ~15% of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of β-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - lungs (80%): cough, hemoptysis, CXR lesion(s)
    - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
    - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - liver (10%): elevated LFTs, U/S or CT findings
    - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
  - highly vascular tumor → bleeding → anemia
  - all have rising or plateau of β-hCG
  - classification of metastatic GTN
    - divided into good prognosis and bad prognosis
      - long duration (>4 mo from antecedent pregnancy)
      - high pre-treatment β-hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood
      - brain or liver metastases
      - prior chemotherapy
      - metastatic disease following term pregnancy
    - good prognosis characterized by the absence of each of these features

**Investigations – For Staging**
- blood work: CBC, electrolytes, creatinine, β-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis, CT abdo/pelvis, CT brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF β-hCG
  - ratio of plasma β-hCG:CSF β-hCG <60 indicates metastases

<table>
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<th>Stage</th>
<th>Findings</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disease confined to uterine corpus</td>
<td>Single agent chemotherapy for low risk disease (WHO score ≤6) 1st line: pulsed – actinomycin D (Act-D) IV q2wk Alternatives: MTX-based regimen 20% of patients need to switch to alternate single-agent regimen due to failure of β-hCG to return to normal Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single agent chemotherapy Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumor</td>
</tr>
<tr>
<td>II</td>
<td>Metastatic disease to genital structures</td>
<td>As above</td>
</tr>
<tr>
<td>III</td>
<td>Metastatic disease to lungs with or without genital tract involvement</td>
<td>As above</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastatic sites including brain, liver, kidney, GI tract</td>
<td>Usually high risk (EMA-CO) with surgical resection of sites of disease Persistence/resistance to chemotherapy Consider radiation for brain mets</td>
</tr>
</tbody>
</table>
Table 26. WHO Prognostic Score for GTD (2011)

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age</td>
<td></td>
</tr>
<tr>
<td>&gt;40</td>
<td>40</td>
</tr>
<tr>
<td>AP</td>
<td></td>
</tr>
<tr>
<td>Mole</td>
<td></td>
</tr>
<tr>
<td>Abortion</td>
<td></td>
</tr>
<tr>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval (end of AP to chemotherapy in months)</td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>4-6</td>
</tr>
<tr>
<td>4-6</td>
<td>7-13</td>
</tr>
<tr>
<td>&gt;13</td>
<td></td>
</tr>
<tr>
<td>hCG IU/l</td>
<td></td>
</tr>
<tr>
<td>&lt;103</td>
<td>103-104</td>
</tr>
<tr>
<td>103-104</td>
<td>104-105</td>
</tr>
<tr>
<td>&gt;105</td>
<td></td>
</tr>
<tr>
<td>Number of Metastases</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1-4</td>
</tr>
<tr>
<td>1-4</td>
<td>5-8</td>
</tr>
<tr>
<td>&gt;8</td>
<td></td>
</tr>
<tr>
<td>Site of Metastases</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>Spleen, kidney</td>
<td></td>
</tr>
<tr>
<td>GI tract</td>
<td></td>
</tr>
<tr>
<td>Brain, liver</td>
<td></td>
</tr>
<tr>
<td>Largest Tumor Mass</td>
<td></td>
</tr>
<tr>
<td>3-5 cm</td>
<td>&gt;5 cm</td>
</tr>
<tr>
<td>Prior Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Single drug</td>
<td></td>
</tr>
<tr>
<td>Two drug</td>
<td></td>
</tr>
</tbody>
</table>

Follow-up (for GTN)
- contraception for all stages to avoid pregnancy during entire follow-up period
- stage I, II, III
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 12 mo
- stage IV
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 24 mo

Common Medications

Table 27. Common Medications

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Action</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acyclovir (Zovirax®)</td>
<td>Antiviral; inhibits DNA synthesis and viral replication</td>
<td>First Episode: 400 mg PO tid x 7-10 d Recurrence: 400 mg PO tid x 5 d</td>
<td>Genital herpes</td>
<td>S/E: headache, GI upset D/I: zidovudine, probenecid</td>
</tr>
<tr>
<td>bromocriptine (Parlodel®)</td>
<td>Dopaminomimetic Agonist at D2R Antagonist at D1R Acts directly on anterior pituitary cells to inhibit synthesis and release of prolactin</td>
<td>Initial: 1.25-2.5 mg PO qhs with food Then: increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response Usual Range: 1.5-15 mg OD For IVF: Initial: 1.25 mg/d PO between days 4-6 of follicular phase Then: 2.5 mg/d until 3 d after onset menstruation</td>
<td>Galactorrhea + amenorrhea Z+ to hyperprolactinemia Prolactin-dependent menstrual disorders and infertility Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas) IVF</td>
<td>S/E: N/V, headache, postural hypotension, somnolence C/I: uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding D/I: domperidone, macrolides, octreotide</td>
</tr>
<tr>
<td>clomiphene citrate (Clomid®)</td>
<td>Increases output of pituitary gonadotropins which induces ovulation</td>
<td>50 mg OD x 5 d Try 100 mg or 160 mg OD if ineffective 3 courses = adequate trial</td>
<td>Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy</td>
<td>S/E: Common – hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz Rare – ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects C/I: pregnancy, liver disease, hormone-dependent tumors, ovarian cyst, undiagnosed vaginal bleeding D/I: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives</td>
</tr>
<tr>
<td>clotrimazole (Lotrimin®)</td>
<td>Antifungal; disrupt fungal cell membrane</td>
<td>Tablet: 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose Cream (1 or 2%): 1 applicator intravaginally qhs x 3-7 d Topical: apply bid x 7 d</td>
<td>Vulvovaginal candidiasis</td>
<td>S/E: vulvar/vaginal burning</td>
</tr>
<tr>
<td>danazol (Danocrine®)</td>
<td>Synthetic steroid that inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties</td>
<td>200-800 mg in 2-3 divided doses Used for 3-6 mo Biannual hepatic U/S required if &gt;6 mo use</td>
<td>Endometriosis 1° menorrhagia/DUB</td>
<td>S/E: weight gain, acne, mild hirsutism, hepatic dysfunction C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia, thromboembolic disease D/I: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives</td>
</tr>
</tbody>
</table>
## Table 27. Common Medications (continued)

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Action</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</th>
</tr>
</thead>
<tbody>
<tr>
<td>doxycycline</td>
<td>Tetracycline derivative; inhibit protein synthesis</td>
<td>100 mg PO bid x ≥ 7 d</td>
<td>Chlamydia, gonococcal infection, syphilis</td>
<td>S/E: GI upset, hepatotoxicity C/I: pregnancy, severe hepatic dysfunction D/I: warfarin, digoxin</td>
</tr>
<tr>
<td>fluconazole (Diflucan&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Antifungal; disrupt fungal cell membrane</td>
<td>150 mg PO x 1 dose</td>
<td>Vulvovaginal candidiasis unresponsive to clotrimazole</td>
<td>S/E: headache, rash, N/V, abdominal pain, diarrhea D/I: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin</td>
</tr>
<tr>
<td>leuprolide (Lupron&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Synthetic GnRH analog Induces reversible hypoestrogenic state</td>
<td>3.75 mg IM q1mo or 11.25 mg IM q3mo Usually ≤ 6 mo, check bone density if &gt; 6 mo Retreatment with Lupron&lt;sup&gt;®&lt;/sup&gt; alone not recommended because of effects on bone density</td>
<td>Endometriosis Leiomyomata DUB Precocious puberty</td>
<td>S/E: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding</td>
</tr>
<tr>
<td>menotropin (Pergonal&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development</td>
<td>75-150 U of FSH and LH IM OD x 7-12 d, then 10,000 U hCG one day after last dose</td>
<td>Infertility</td>
<td>S/E: bloating, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumor), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding</td>
</tr>
<tr>
<td>metronidazole (Flagyl&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Bactericidal; forms toxic metabolites which damage bacterial DNA</td>
<td>2 g PO x 1 dose or 500 mg PO bid x 7 d</td>
<td>Bacterial vaginosis, trichomonas vaginitis</td>
<td>S/E: headache, diziness, N/V, diaphoresis, disulfiram-like reaction (flushing, tachycardia, V/V) C/I: pregnancy (1st trimester) D/I: cisapride, warfarin, cimetidine, lithium, alcohol, amidotride, milk thistle, carbamazepine</td>
</tr>
<tr>
<td>oxybutinin (Ditropan&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Anticholinergic – relaxes bladder smooth muscle, inhibits involuntary detrusor contraction</td>
<td>5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d</td>
<td>Overactive bladder (urge incontinence)</td>
<td>S/E: dry mouth/eyes, constipation, palpitations, urinary retention, diziness, headache C/I: glaucoma, GI liens, severe colitis, obstructive urethra, use with caution if impaired hepatic/renal function</td>
</tr>
<tr>
<td>tolterodine (Detrol&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Anticholinergic</td>
<td>1-2 mg PO bid</td>
<td>Overactive bladder (urge incontinence)</td>
<td>S/E: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain C/I: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function</td>
</tr>
<tr>
<td>tranexamic acid (Cyklokapron&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Anti-fibrinolytic, reversibly inhibits plasminogen activation</td>
<td>1.5 g tid-qid for first 4 d of cycle Max 4 g/d Ophthalmic check if used for several wk</td>
<td>Menorrhagia</td>
<td>S/E: N/V, diziness, rare cases of thrombosis, abdominal pain, MSK pain C/I: thromboembolic disease, acquired disturbances of color vision, subarachnoid hemorrhage, age &lt;15 yr</td>
</tr>
<tr>
<td>urofollitropin (Metrodin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>FSH</td>
<td>75 U/d SC x 7-12d</td>
<td>Ovulation induction in PCOS</td>
<td>S/E: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumor), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding</td>
</tr>
<tr>
<td>combined oral contraceptive pill (OCP)</td>
<td>Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration</td>
<td></td>
<td>Contraception Disorders of menstruation</td>
<td>See Tables 8-12</td>
</tr>
<tr>
<td>intrauterine device (IUD)</td>
<td>Copper IUD: mild foreign body reaction in endometrium which is toxic to sperm and alters sperm motility Progestosterone-releasing IUD: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation</td>
<td>Contraceptive effects last 5 yr</td>
<td>Same as above</td>
<td>See Table 8-12</td>
</tr>
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**Basics of Hematology**

- over $10^{11}$ blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies
- lifespan of mature cells in blood
  - erythrocytes (120 d), neutrophils (~1 d), platelets (10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - spleen: part of reticuloendothelial system, removes aged RBCs, removes antibody-coated bacteria/cells, site of antibody production
  - thymus: site of T-cell maturation, involutes with age
  - lymph nodes: sites of B and T-cell activation (adaptive immune response)

---

**Hematopoietic Stem Cell**

- **Megakaryocyte/erythrocyte precursor**
  - Megakaryoblast
  - Proerythroblast
  - Polychromatic erythroblast
  - Platelets
  - Erythrocyte

- **Myeloid precursor**
  - Monoblast
  - Monoerythroblast
  - Macrophage

- **Lymphoid precursor**
  - Myeloblast
  - Basophil
  - Eosinophil
  - Neutrophil
  - B-Cell
  - T-Cell

**Granulocytes**

---

**Acronyms**

- **AFib** atrial fibrillation
- **AFLP** acute fatty liver of pregnancy
- **AIHA** autoimmune hemolytic anemia
- **ALL** acute lymphoblastic leukemia
- **AML** acute myeloid leukemia
- **ANC** absolute neutrophil count
- **APC** activated protein C resistance
- **APS** antiphospholipid antibody syndrome
- **CSC** complete blood count
- **CML** chronic myeloid leukemia
- **DIC** disseminated intravascular coagulation
- **EPO** erythropoietin
- **G6PD** glucose-6-phosphate dehydrogenase
- **Hb** hemoglobin
- **Hct** hematocrit
- **HIT** heparin-induced thrombocytopenia
- **HUS** hemolytic uremic syndrome
- **RAEB** refractory anemia with excess blasts
- **RARS** refractory anemia with ringed sideroblasts
- **RBC** red blood cells
- **RCMD** refractory cytopenia with multilineage dysplasia
- **RCMD-RS** refractory cytopenia with multilineage dysplasia and ringed sideroblasts
- **RDW** RBC distribution width
- **SPEP** serum protein electrophoresis
- **TTP** thrombotic thrombocytopenic purpura
- **UH** unfractionated heparin
- **UPEP** urine protein electrophoresis
- **VTE** venous thromboembolism
- **WBCC** white blood cell count
- **WHO** World Health Organization
### Complete Blood Count

#### Table 1. Common Terms Found on CBC

<table>
<thead>
<tr>
<th>Test</th>
<th>Definition</th>
<th>Normal Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell (RBC) Count</td>
<td>The number of RBCs per volume of blood</td>
<td>4.2-6.9 x 10^6/mm³</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>Amount of oxygen-carrying protein in the blood</td>
<td>13-18 g/dL (male)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-16 g/dL (female)</td>
</tr>
<tr>
<td>Hematocrit (Hct)</td>
<td>Percentage of a given volume of whole blood occupied by packed RBCs</td>
<td>45%-62% (male)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37%-48% (female)</td>
</tr>
<tr>
<td>Mean Corpuscular Volume (MCV)</td>
<td>Measurement of size of RBCs</td>
<td>80-100 µm³</td>
</tr>
<tr>
<td>Mean Corpuscular Hb (MCH)</td>
<td>Amount of oxygen-carrying Hb inside RBCs</td>
<td>27-32 pg/cell</td>
</tr>
<tr>
<td>Mean Corpuscular Hb Concentration (MCHC)</td>
<td>Average concentration of Hb inside RBCs</td>
<td>32%-36%</td>
</tr>
<tr>
<td>RBC Distribution Width (RDW)</td>
<td>Measurement of variance in RBC size</td>
<td>11.0%-15.0%</td>
</tr>
<tr>
<td>White Blood Cell (WBC) Count</td>
<td>The number of WBCs per volume of blood</td>
<td>4,300-10,800/mm³</td>
</tr>
<tr>
<td>WBC Differential</td>
<td>Includes neutrophils, eosinophils, basophils, lymphocytes, and monocytes</td>
<td></td>
</tr>
<tr>
<td>Platelet Count</td>
<td>The number of platelets per volume of blood</td>
<td>150,000-400,000/mm³</td>
</tr>
<tr>
<td>Mean Platelet Volume (MPV)</td>
<td>Measurement of platelet size</td>
<td></td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>Immature RBCs that contain no nucleus but have residual RNA</td>
<td>Normally make up 1% of total RBC count</td>
</tr>
</tbody>
</table>

*Normal values may vary depending on site and age

#### Approach to Interpreting a CBC

1. Consider values in the context of individual's baseline
   - up to 5% of population without disease may have values outside “normal” range
   - an individual may display a clinically significant change from their baseline without violating “normal” reference range
2. Is one cell line affected or are several?
   - if all lines are low: pancytopenia (see Pancytopenia, H8)
   - if RBCs and platelets are low: consider a MAHA (see H22)
   - if single cell line affected: see corresponding section in Common Presenting Problems, H6

#### Blood Film Interpretation

**RED BLOOD CELLS**

**Size**
- microcytic (MCV <80), normocytic (MCV = 80-100), macrocytic (MCV >100)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, hemolytic anemias, myelofibrosis, blood transfusion

**Color**
- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
  - iron deficiency anemia, anemia of chronic inflammation, sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
  - increased RBC production by bone marrow

**Shape**
- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, myelofibrosis
Table 2. Common Erythrocyte Shapes

<table>
<thead>
<tr>
<th>Shape</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discocyte</td>
<td>Biconcave disc</td>
<td>Normal RBC</td>
</tr>
<tr>
<td>Spherocyte</td>
<td>Spherical RBC (due to loss of membrane)</td>
<td>Hereditary spherocytosis, immune hemolytic anemia, post-transfusion</td>
</tr>
<tr>
<td>Elliptocyte/Ovalocyte</td>
<td>Oval-shaped, elongated RBCs</td>
<td>Hereditary elliptocytosis, megaloblastic anemia, myelofibrosis, iron-deficiency, MDS</td>
</tr>
<tr>
<td></td>
<td>• Elliptocytes: the RBC long axis is ≥2x the length of the short axis</td>
<td>(myelodysplastic syndrome)</td>
</tr>
<tr>
<td></td>
<td>• Ovalcytes: the RBC long axis is &lt;2x the length of the short axis</td>
<td></td>
</tr>
<tr>
<td>Schistocyte (helmet cell)</td>
<td>Fragmented cells (due to traumatic disruption of membrane)</td>
<td>Microangiopathic hemolytic anemia (HUS/TTP, DIC, preeclampsia, HELLP, malignant HTN), vasculitis, glomerulonephritis, prosthetic heart valve</td>
</tr>
<tr>
<td>Sickle Cell</td>
<td>Sickle-shaped RBC (due to polymerization of hemoglobin S)</td>
<td>Sickle cell disorders: HbSC, HbSS</td>
</tr>
<tr>
<td>Codocyte (target cell)</td>
<td>“Bull’s eye” on dried film</td>
<td>Liver disease, hemoglobin SC, thalassemia, Fe deficiency, asplenia</td>
</tr>
<tr>
<td>Dacrocyte (teardrop cell)</td>
<td>Single pointed end, looks like a teardrop</td>
<td>Myelofibrosis, thalassemia major, megaloblastic anemia</td>
</tr>
<tr>
<td>Acanthocyte (spur cell)</td>
<td>Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids)</td>
<td>Severe liver disease (spur cell anemia), starvation/anoxia, post-splenectomy</td>
</tr>
<tr>
<td>Echinocyte (burr cell)</td>
<td>RBC with numerous regularly spaced, small spiny projections</td>
<td>Uremia, HUS, burns, cardiopulmonary bypass, post-transfusion, storage artifact</td>
</tr>
<tr>
<td>Rouleaux Formation</td>
<td>Aggregates of RBC resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)</td>
<td>Pregnancy: most common cause; due to physiological increase in fibrinogen, inflammatory conditions: due to polyclonal immunoglobulins Plasma cell dyscrasias: due to monoclonal paraproteinaemia, e.g. multiple myeloma, macroglobulinemia Storage artifact</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, and low platelet count; HUS = hemolytic uremic syndrome; TTP = thrombotic thrombocytopenic purpura.
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

Table 3. RBC Inclusions

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus</td>
<td>Present in erythroblasts (immature RBCs)</td>
<td>Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, MPNs (MF)</td>
</tr>
<tr>
<td>Heinz Bodies</td>
<td>Denatured and precipitated hemoglobin</td>
<td>G6PD deficiency (post-exposure to oxidant), thalassemia, unstable hemoglobins</td>
</tr>
<tr>
<td>Howell-Jolly Bodies</td>
<td>Small nuclear remnant resembling a pyknotic nucleus</td>
<td>Post-splenectomy, hyposplenism (sickle cell disease), neonates, megaloblastic anemia</td>
</tr>
<tr>
<td>Basophilic Stippling</td>
<td>Deep blue granulations indicating ribosome aggregation</td>
<td>Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, hereditary (pyrimidine 5’nucleotidase deficiency)</td>
</tr>
<tr>
<td>Sideroblasts</td>
<td>Erythrocytes with Fe containing granules in the cytoplasm</td>
<td>Hereditary, idiopathic, drugs, hypothyroidism (see Sideroblastic Anemia, H16), myelodysplastic syndrome</td>
</tr>
</tbody>
</table>

BM = bone marrow; MF = myelofibrosis; MPN = myeloproliferative neoplasm.
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012.
WHITE BLOOD CELLS
- lymphocytes: comprise 30-40% of WBCs; great variation in "normal" lymphocyte morphology
- neutrophils
  - normally only mature neutrophils (with 3-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
  - hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B12 or folate deficiency)
  - left shift (increased granulocyte precursors)
    - seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, myeloproliferative neoplasms (CML, MF)
- blasts
  - immature, undifferentiated precursors; associated with acute leukemia, MDS, G-CSF (growth factor that stimulates neutrophil production) use

PLATELETS
- small, purple, anuclear cell fragments

Table 4. Abnormal White Blood Cells on Film

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed-Sternberg Cell</td>
<td>Giant, multinucleated B-lymphocyte, only seen with bone marrow specimens</td>
<td>Primarily Hodgkin lymphoma, also seen in some non-Hodgkin lymphoma, CLL, and EBV infection</td>
</tr>
<tr>
<td>Smudge Cell</td>
<td>Lymphocytes damaged during blood film preparation indicating cell fragility</td>
<td>Chronic lymphocytic leukemia (CLL) and other lymphoproliferative disorders Pathognomonic in EBV infection</td>
</tr>
<tr>
<td>Auer Rod</td>
<td>Clumps of granular material that form long needles in the cytoplasm of myeloblasts</td>
<td>Pathognomonic for acute myeloid leukemia (AML)</td>
</tr>
</tbody>
</table>

EBV = Epstein-Barr virus
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

Bone Marrow Aspiration and Biopsy

- sites: posterior iliac crest, sternum
- analyses: most often done together; exception is in follow-up of conditions or diagnosis of CML where aspiration alone could suffice
  - aspiration: takes a fluid marrow sample for cellular morphology, flow cytometry, cytogenetics, molecular studies, microbiology (C&S, AFB, PCR)
  - biopsy: takes a sample of intact bone marrow to assess histology and immunohistochemistry

Indications
- unexplained CBC abnormalities
- diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, solid tumors
- diagnosis and staging of lymphoma or solid tumors
- evaluate iron metabolism and stores (gold standard, but rarely done)
- evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher's disease)
- evaluate fever of undetermined origin, suspected mycobacterial, fungal/parasitic infections, or granulomatous disease
- unexplained splenomegaly
- confirm normal bone marrow in potential allogenic hematopoietic cell donor

Contraindications
- absolute: untreated hemophilia, severe DIC, infection over skin site
- relative: platelet count <10, recent warfarin use with INR >2.0, liver disease with associated coagulopathy
- thrombocytopenia is not a contraindication; may need platelet transfusion prior to procedure
Common Presenting Problems

Anemia

Definition
- a decrease in red blood cell (RBC) mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
  - adult males: Hb <13 g/dL or Hct <0.41
  - adult females: Hb <12 g/dL or Hct <0.36

Low MCV (<80)
- Iron deficiency
- Thalassemia
- Anemia of chronic disease
- Sideroblastic anemia
- Lead poisoning

Normal MCV (80-100)

High MCV (>100)
- Megaloblastic
  - B12 deficiency
  - Folate deficiency
  - Drugs that impair DNA synthesis (methotrexate, sulfa, chemotherapy)
- Non-megaloblastic
  - Liver disease
  - Alcoholism
  - Reticulocytosis (see high reticulocyte, on left)
  - Hypothyroidism
  - Myelodysplasia

Low Hemoglobin

High reticulocyte
- Increased destruction (retics >2-3%)

Low reticulocyte
- Decreased production (retics <2%)

Hemolysis
- Inherited
  - Hemoglobinopathy (sickle cell disease, thalassemia, unstable Hb)
  - Membrane (spherocytic)
  - Metabolic (HMP shunt, glycolytic pathway)
- Acquired
  - Immune (Coombs positive, drug-related, cold agglutinin)
  - Infection (malaria)
  - Microniopagaphic hemolytic anemias (DIC, TTP, HUS, HELLP)
  - Oxidative/drug-related

Bleeding
- GI
- GU
- Other

Pancytopenia
- Aplastic anemia
- MDS
- Myelofibrosis
- Leukemia
- TB
- Amyloidosis, sarcoidosis
- Drugs (e.g. chemotherapy)

Non-pancytopenia
- Anemia of chronic disease
- Renal/liver disease

Low reticulocyte
- Decreased production (retics <2%)

HMP = hexose monophosphate

Figure 2. Approach to anemia – classification by size of RBC

Clinical Features
- history
  - symptoms of anemia: fatigue, malaise, weakness, dyspnea, decreased exercise tolerance, palpitations, headache, dizziness, tinnitus, syncope
  - acute vs. chronic, bleeding, systemic illness, diet, alcohol, family history
  - menstrual history: menorrhagia, menometrorrhagia, dysfunctional uterine bleeding
  - rule out pancytopenia (recurrent infection, mucosal bleeding/easy bruising)
- physical signs
  - HEENT: pallor in mucous membranes, palmar creases and conjunctiva at Hb <9.0 g/dL, ocular bruits at Hb <5.5 g/dL, angular cheilosis, jaundice
  - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
  - dermatologic: pallor in palmar skin creases at Hb <7.5 g/dL, jaundice (if due to hemolysis), nail changes, glossitis

Investigations
- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential (MCV, RDW, RBC count)
- reticulocyte count – very useful to evaluate for blood cell production problems but must be corrected for anemia
- blood film
- rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
- additional laboratory investigations as indicated (see Microcytic Anemia, H13, Normocytic Anemia, H17, Hemolytic Anemia, H18, and Macrocytic Anemia, H24)

Erythrocytosis

Definition
- an increase in the number of RBCs: Hb >18.5 g/dL or Hct >52% (males); Hb >16.5 g/dL or Hct >47% (females and African males)

Etiology
- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, "stress" (Gaisböck's syndrome)
- absolute erythrocytosis
Table 5. Etiology of Erythrocytosis

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Inappropriate Production of Erythropoietin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia Vera (PV)</td>
<td>Physiologic (poor tissue oxygenation/hypoxia)</td>
<td>Tumors</td>
</tr>
<tr>
<td>(see Polycythemia Vera, H41)</td>
<td>Carbon monoxide poisoning</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Heavy smoking</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>High altitude</td>
<td>Cerebellar hemangioblastoma</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>COPD</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Sleep apnea</td>
<td>Uterine leiomymoma</td>
</tr>
<tr>
<td></td>
<td>Pulmonary HTN</td>
<td>Ovarian tumor</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>R to L shunt (Eisenmenger syndrome)</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>RBC defects (Hb with increased O₂ affinity,</td>
<td>Polycystic kidney disease</td>
</tr>
<tr>
<td></td>
<td>methemoglobinemia)</td>
<td>Post-kidney transplant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Androgens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exogenous erythropoietin</td>
</tr>
</tbody>
</table>

Clinical Features
- secondary to high red cell mass and hyperviscosity
  - headache, dizziness, tinnitus, visual disturbances, hypertensive symptoms
  - symptoms of angina, congestive heart failure, aquagenic pruritus
  - thrombosis (venous or arterial) or bleeding (abnormal platelet function)
- physical findings
  - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

Investigations
- serum erythropoietin (EPO): increased EPO suggests autonomous production or hypoxia, and is used to rule out PV
  - search for tumor as source of EPO as indicated (e.g. abdominal U/S, CT head)
  - JAK-2 mutation analysis: positive in >96% of cases of PV
  - only send if low/normal EPO level
- ferritin (iron deficiency can mask the diagnosis)

Treatment
- if primary: see Polycythemia Vera, H41
- if secondary: treat underlying cause
  - O₂ for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumors
  - often cardiologists will not treat high HCT in cyanotic patients (or will have high threshold)

Thrombocytopenia

Definition
- platelet count <150,000/mm³

Clinical Features
- history: bleeding gums, epistaxis, bleeding post-surgical procedures, metronomorrhagia
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura
  - hemarthrosis and deep muscle hematomas are rarely initial signs in patients with primary hemostatic disorders
- see Disorders of Primary Hemostasis, H27, for complications

Investigations
- CBC and differential
- blood film
  - decreased production: other cell line abnormalities, blasts, hypersegmented PMNs, leukoerythroblastic changes
  - increased destruction: large platelets, schistocytes (seen in MAHA)
  - rule out platelet clumping
- workup for nutritional deficiencies: B₁₂, RBC folate
- PT/INR, aPTT and fibrinogen if DIC suspected
- LFTs

Treatments
- life threatening bleeding: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see Immune Thrombocytopenic Purpura, H27

Must rule out factitious thrombocytopenia: platelet clumping (secondary to EDTA antibodies from collection tube). This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA)

In hospitalized patients, drugs and infection account for the majority of cases of thrombocytopenia.
**Thrombocytopenia**

**Definition**
- platelet count >400,000/mm³
- primary thrombocytopenia: due to myeloproliferative neoplasms (e.g. CML, polycythemia vera [PV], primary myelofibrosis, essential thrombocytosis [ET]; rarely associated with MDS)
- reactive/secondary thrombocytopenia: acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms, ischemic injury); much more common than primary

**Clinical Features**
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative neoplasms (MPNs)

**Investigations**
- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- JAK-2 PCR (mutation in ~50% of ET)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS

**Treatment**
- primary: ASA ± cytoreductive agents
- secondary: treat underlying cause

---

**Pancytopenia**

**Definition**
- a decrease in all hematopoietic cell lines

**Clinical Features**
- anemia: fatigue
- leukopenia: recurrent infections
- thrombocytopenia: mucosal bleeding and ecchymoses

**Investigations**
- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- JAK-2 PCR (mutation in ~50% of ET)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS
Neutrophilia

Definition
• different guidelines, but absolute neutrophil count (ANC) >7.7 x 10^9/L

Etiology
• primary neutrophilia
  ▪ chronic myeloid leukemia (CML)
  ▪ other myeloproliferative disorders: PV, essential thrombocytosis (ET), myelofibrosis
  ▪ hereditary neutrophilia (autosomal dominant)
  ▪ chronic idiopathic neutrophilia in otherwise healthy patients
  ▪ leukocyte adhesion deficiency
• secondary neutrophilia
  ▪ smoking: most common cause of mild neutrophilia
  ▪ infection: leukocytosis with left shift ± toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
  ▪ inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, burns
  ▪ malignancy: hematologic (i.e. marrow invasion by tumor) and non-hematologic (especially large cell lung cancer)
  ▪ stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  ▪ medications: glucocorticoids, β-agonists, lithium

Clinical Features
• look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  ▪ including lymph nodes and organomegaly
• examine oral cavity, teeth, peri-rectal area, genitals, and skin for signs of infection

Investigations
• CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
• blood film: Döhle bodies, toxic granulation, cytoplasmic vacuoles in infection
• review other blood counts
• may require bone marrow biopsy if MPN suspected

Treatment
• directed at underlying cause

Neutropenia

Definition
• mild: ANC 1,000-1,500/mm^3
• moderate: ANC 500-1,000/mm^3 (risk of infection starts to increase)
• severe: ANC <500/mm^3
• profound: ANC <100/mm^3 for >7 d
**Etiology**

**Table 6. Etiology of Neutropenia**

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Peripheral Destruction</th>
<th>Excessive Margination (Transient Neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td>Anti-neutrophil antibodies</td>
<td>Idiopathic (most common)</td>
</tr>
<tr>
<td>Viral hepatitis, EBV, HIV, TB, typhoid, malaria</td>
<td>Spleen or lung trapping</td>
<td>Overwhelming bacterial infection</td>
</tr>
<tr>
<td><strong>Hematological Diseases</strong></td>
<td>Autoimmune disorders: RA (Felty’s syndrome), SLE</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>Idiopathic, aplastic anemia, myelofibrosis, BM infiltration</td>
<td>Granulomatosis with polyangitis (formerly Wegener’s)</td>
<td>Racial variation (e.g. African or Ashkenazi Jewish descent)</td>
</tr>
<tr>
<td><strong>Drug-Induced</strong></td>
<td>Drugs: haptens (e.g. α-methyldopa)</td>
<td></td>
</tr>
<tr>
<td>Alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, anti-thyroid drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toxins/Chemicals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose radiation, benzene, DDT</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nutritional Deficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B12, folate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Idiopathic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional neutropenia, benign cyclic neutropenia, cyclical</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Features**
- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. *S. aureus*, gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth, and throat following colonization by opportunistic organisms
- avoid digital rectal exam

**Investigations**
- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

**Treatment**
- regular dental care: chronic gingivitis and recurrent stomatitis major sources of morbidity
- febrile neutropenia (see Infectious Diseases, ID46)
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, methotrexate)

**Lymphocytosis**

**Definition**
- absolute lymphocyte count >4 x 10⁹/L

**Etiology**
- infection
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
  - physiologic response to stress (e.g. trauma, status epilepticus)
  - hypersensitivity (e.g. drugs, serum sickness)
  - autoimmune (e.g. rheumatoid arthritis)
  - neoplasm (e.g. ALL, CLL, lymphoma)

**Investigations**
- peripheral smear

**Treatment**
- treat underlying cause

**Lymphopenia**

**Definition**
- absolute lymphocyte count <1,500/mm³

**Etiology**
- idiopathic CD4+ lymphocytopenia
- radiation
- HIV/AIDS, hepatitis B, hepatitis C
- malignancy/chemotherapeutic agents
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)
Clinical Features
- opportunistic infections (see Infectious Diseases, ID46)

Treatment
- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis
  (see Infectious Diseases, ID48)

Eosinophilia

Definition
- absolute eosinophil count >500/mm³

Etiology
- primary: due to clonal bone marrow disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome
    - 6 mo of eosinophilia with no other detectable causes (often with clonal molecular abnormality)
    - can involve heart, bone marrow, CNS
- secondary
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes:
    - polyarteritis nodosa, see Rheumatology, RH19
    - respiratory causes (asthma, eosinophilic pneumonia, Churg-Strauss)
    - cholesterol emboli
    - hematologic malignancy: see Chronic Myeloid Leukemia, H40 and Hodgkin Lymphoma, H45
    - adrenal insufficiency, see Endocrinology, E35
    - medications (penicillins)

Treatment
- treat underlying cause

Agranulocytosis

Definition
- severe depletion of granulocytes (neutrophils, eosinophils, basophils) from the blood and granulocyte precursors from bone marrow

Etiology
- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine, and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors

Clinical Features
- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

Prognosis
- high fatality without vigorous treatment

Investigations/Treatment
- discontinue offending drug
- pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture, and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider bone marrow aspirate and biopsy if cause unclear
- consider G-CSF

Leukemoid Reactions

- blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
- leukocytosis >50,000/mm³, marked left shift (myelocytes, metamyelocytes, bands in peripheral blood smear)

Etiology
- important to rule out CML
- differential diagnosis:
  - myeloid progenitors: pneumonia, other acute bacterial infections, intoxications, burns, malignant disease, severe hemorrhage or hemolysis
  - lymphoid progenitors: pertussis, TB, infectious mononucleosis
  - monocytic progenitors: TB
Approach to Lymphadenopathy

History
• constitutional/B-symptoms: seen in TB, lymphoma, other malignancies
• exposures: cats (cat scratch – *Bartonella henselae*), ticks (Lyme disease – *Borrelia burgdorferi*), high risk behaviors (HIV)
• joint pain/swelling, rashes (connective tissue disorder)
• pruritus (seen in Hodgkin lymphoma)
• medications (can cause serum sickness → lymphadenopathy)

Physical Exam
• basic assessment: occipital, preauricular, submandibular, cervical, supra-/infra-clavicular, axillary, epitrochlear, inguinal, popliteal nodes
  • characteristics of lymph nodes
  • look for signs of infection in regions which lymph nodes drain
• determine if lymphadenopathy is localized or generalized
• localized: typically reactive or neoplastic
  • cervical (bacterial/mycobacterial infections, ENT malignancies, metastatic cancer)
  • supraclavicular
    • right (mediastinal, bronchogenic, esophageal cancer)
    • left (gastric, gall bladder, pancreas, renal, testicular/ovarian cancer)
  • axillary (cat scratch fever, breast cancer, metastatic cancer)
  • epitrochlear (infections, sarcoidosis, lymphoma)
  • lower/inguinal (STDs, skin, cervix, vulva/penis, rectum/anus cancer)
• generalized: see Table 8
• thorough examination required to assess for systemic disease

Investigations
• CBC and differential, blood film
• ± tuberculin test, HIV RNA, RPR/VDRL, monospot/EBV serology, ANA, imaging as indicated
• if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → biopsy)
• excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
• in difficult to access areas (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
• FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (use excisional biopsy instead)
  • helpful for recurrence of solid tumor malignancy

Table 7. Inflammatory vs. Neoplastic Lymph Nodes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>Rubbery</td>
<td>Firm/hard</td>
</tr>
<tr>
<td>Mobility</td>
<td>Mobile</td>
<td>Matted/immobile</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Tender</td>
<td>Non-tender</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;2 cm</td>
<td>&gt;2 cm</td>
</tr>
</tbody>
</table>

*Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender*

Table 8. Differential Diagnosis of Generalized Lymphadenopathy

<table>
<thead>
<tr>
<th>Reactive Diagnosis</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial (TB, Lyme, brucellosis, cat scratch disease, syphilis)</td>
<td>Collagen disease (RA, dermatomyositis, SLE, vasculitis, Sjögren’s)</td>
<td>Lymphoproliferative disorder/lymphoma</td>
</tr>
<tr>
<td>Viral (EBV, CMV, HIV)</td>
<td>Drug hypersensitivity</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Parasitic (toxoplasmosis)</td>
<td>Sarcoidosis, amyloidosis</td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Fungal (histoplasmosis)</td>
<td>Serum sickness</td>
<td></td>
</tr>
</tbody>
</table>
Approach to Splenomegaly

### Table 9. Differential Diagnosis of Splenomegaly

<table>
<thead>
<tr>
<th>Increased Demand for Splenic Function</th>
<th>Congestive</th>
<th>Infiltrative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spherocytosis</td>
<td>Infectious</td>
<td>Cirrhosis</td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
<td>Bacterial endocarditis</td>
<td>Splenic vein thrombosis</td>
</tr>
<tr>
<td>Hemolyis</td>
<td>TB</td>
<td>Portal vein obstruction</td>
</tr>
<tr>
<td>Sequestration crisis</td>
<td>HIV/AIDS</td>
<td>(including right heart failure)</td>
</tr>
<tr>
<td>Nutritional anemias</td>
<td>EBV</td>
<td></td>
</tr>
<tr>
<td>Elliptocytosis</td>
<td>Malaria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histoplasmosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leishmaniasis</td>
<td></td>
</tr>
<tr>
<td>Infiltrative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Non-Malignant</td>
<td></td>
</tr>
<tr>
<td>Splenic vein thrombosis</td>
<td>Benign metaplasia</td>
<td></td>
</tr>
<tr>
<td>Portal vein obstruction</td>
<td>Amyloidosis</td>
<td></td>
</tr>
<tr>
<td>(including right heart failure)</td>
<td>Sarcoidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lysosomal storage diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Gaucher’s, Niemann-Pick)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glycogen storage diseases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematological</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neoplasm (malignant, non-malignant)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Autoimmune</td>
<td></td>
</tr>
</tbody>
</table>

The underlined conditions cause massive splenomegaly (spleen crosses midline or reaches pelvis)

### History
- constitutional symptoms, feeling of fullness in LUQ
- signs or symptoms of infection or malignancy
- history of liver disease, hemolytic anemia, or high-risk exposures

### Physical Exam
- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell's sign, Traube’s space, Nixon’s method) and palpation
- associated lymphadenopathy or hepatomegaly
- signs of CHF

### Investigations
- CBC and differential, blood film
- as indicated: liver enzymes/liver function tests, reticulocyte count, Monospot®, haptoglobin, LDH, infectious, and autoimmune workup
- imaging
  - ultrasound of abdomen/liver to rule out cirrhosis and portal vein thrombosis
  - echo for cardiac function
  - CT to rule out lymphoma

### Microcytic Anemia
- MCV <80 fL
- see Figure 2, Approach to Anemia, H6

### Table 10. Iron Indices and Blood Film in Microcytic Anemia (MCV<80)

<table>
<thead>
<tr>
<th>Lab Tests</th>
<th>Blood Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>Hypochromic, microcytic</td>
</tr>
<tr>
<td>Serum Iron</td>
<td>Normocytic/microcytic</td>
</tr>
<tr>
<td>TIBC</td>
<td>Dual population</td>
</tr>
<tr>
<td>RDW</td>
<td>Basophilic stippling</td>
</tr>
</tbody>
</table>

### Iron Metabolism

#### Iron Intake (Dietary)
- average North American adult diet = 10-20 mg iron (Fe) daily
- absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males have positive Fe balance; up to 20% of menstruating females have negative Fe balance

### Causes of Splenomegaly
- CHINA
- Cirrhosis/Congestion (portal HTN)
- Hematological
- Infectious
- Neoplasm (malignant, non-malignant)
- Autoimmune

### Does This Adult Patient Have Splenomegaly?
- From The Rational Clinical Examination
- JAMA 2009; http://www.jamaevidence.com/content/3487289
- Study: Systematic review of articles assessing the sensitivity and specificity of clinical exam maneuvers for detecting splenomegaly.
- Results: On percussion, Nixon sign had a positive likelihood ratio (+LR) of 3.6 (95% CI 1.8-7.3) and a negative likelihood ratio (-LR) of 0.47 (95% CI 0.29-0.64). Percussion of Traube’s space had a +LR of 2.3 (95% CI 1.8-2.9) and -LR of 0.48 (95% CI 0.39-0.60), while Castell sign had a +LR of 1.2 (95% CI 0.98-1.6) and -LR of 0.45 (95% CI 0.19-1.1). On palpation, supine 1-handed palpation had a +LR of 6.5 (95% CI 3.1-1.5) and -LR of -0.41 (95% CI 0.30-0.57), while Middleton hooking maneuver had a +LR of 0.2 (95% CI 0.5-1.2) and -LR of 0.41 (95% CI 0.19-0.8). On palpation, supine 1-handed palpation had a +LR of 6.5 (95% CI 3.1-1.5) and -LR of 0.16 (95% CI 0.06-0.32).
- Conclusions: Palpation may have greater accuracy than percussion, but may be best when both are used in tandem. Specifically, Nixon sign and supine one-handed palpation are the most accurate, respectively.
Iron Indices

- bone marrow aspirate: gold standard test for iron stores (rarely done)
- serum ferritin: most important blood test for iron stores
  - decreased in iron deficiency anemia
  - elevated in:
    - infection, inflammation, malignancy
    - liver disease, hyperthyroidism, and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
  - virtually all serum iron is bound to transferrin, only a trace is free or complexed in ferritin
- TIBC: total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - high specificity for decreased iron, low sensitivity
- saturation: serum Fe divided by TIBC, expressed as a proportion or a percentage
  - low in iron deficiency anemia
- sTfR
  - reflects the availability of iron at the tissue level
  - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some is cleaved off and is present in circulation as sTfR
  - in iron deficient states more transferrin receptor is expressed on erythroblasts leading to an increase in sTfR
  - low in reduced erythropoiesis and iron overload
  - useful in determining iron deficiency in the setting of chronic inflammatory disorders (see Iron Deficiency Anemia, H15)

Iron Absorption and Transport

- dietary iron is absorbed in the duodenum (impaired by IBD, celiac disease, etc.)
- in circulation the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages of the reticuloendothelial system and hepatocytes) to RBC precursors in the bone marrow

Iron Levels

- hepcidin that regulates systemic iron levels
  - a hormone produced by hepatocytes
  - binds to iron exporter ferroportin on duodenal enterocytes and reticuloendothelial cells, and induces its degradation thereby inhibiting iron export into the circulation
  - hepcidin production is increased in states of inflammation (thereby mediating anemia of chronic inflammation) or iron overload, and decreased in states where erythropoiesis is increased (e.g. hemolysis) or oxygen tension is low

Iron Storage

- ferritin
  - ferric iron (Fe$^{3+}$) complexed to a protein called apoferritin (hepatocytes are main ferritin storage site)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated despite low Fe stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is main source of hemosiderin storage

Figure 5. Iron metabolism
Iron Deficiency Anemia

- see *Pediatrics*, P47
- most common cause of anemia in North America

Etiology
- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
  - decreased supply: dietary deficiencies (rarely the only etiology)
    - cow’s milk (infant diet)
    - “tea and toast” diet (elderly)
    - absorption imbalances
    - post-gastrectomy
    - malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis)
- increased losses
  - obvious causes: menorrhagia, abnormal uterine bleeding, frank GI bleed
  - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - intravascular (e.g. PNH, cardiac valve RBC fragmentation)
    - extravascular (e.g. immune hemolytic anemias)

Clinical Features
- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see *Anemia*, H6
- brittle hair, nail changes (brittle, koilonychia)
- Plummer-Vinson syndrome: dysphagia (esophageal webs), glossitis, angular stomatitis (inflammation and fissuring at the corners of the mouth)
- pica (appetite for non-food substances e.g. ice, paint, dirt)

Investigations
- iron indices, including soluble transferrin receptor
  - low ferritin (<45 µg/L) is diagnostic of iron deficiency
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup (Figure 6)
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms, anisocytosis
  - target cells (thin)
- bone marrow (gold standard but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation

Table 11. The Utility of Ferritin in the Diagnosis of Iron Deficiency Anemia

<table>
<thead>
<tr>
<th>Ferritin (µg/L)</th>
<th>Likelihood ratio for iron deficiency anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;100</td>
<td>0.13</td>
</tr>
<tr>
<td>45-100</td>
<td>0.46</td>
</tr>
<tr>
<td>18-45</td>
<td>3.12</td>
</tr>
<tr>
<td>≤18</td>
<td>41.47</td>
</tr>
</tbody>
</table>

*Am J Med 1990;88:205-209*

Patient with microcytic anemia

- Ferritin ≤45 µg/ml
  - Iron deficiency anemia
  - Assess other iron indices
  - ↑ TIBC, ↓ serum Fe, ↓ saturation

- Ferritin 46-99 µg/ml
  - Any other result:
    - Order sTfR
    - ↑ TIBC, ↑ serum Fe, ↑ saturation

- Ferritin ≥100 µg/ml
  - NO iron deficiency anemia
  - ↓ TIBC, ↓ serum Fe, ↓ saturation
  - ↓ sTfR

Figure 6. Approach to interpreting iron indices

Adapted from: *Am Fam Physician* 2007;75:671-678

Treatment
- treat underlying cause
- supplementation
  - oral (tablets, syrup)
    - ferrous sulphate 325 mg tid, ferrous gluconate 300 mg tid, or ferrous fumarate 300 mg tid
    - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - oral iron should be taken with citrus juice to enhance absorption
  - IV (iron sucrose or dextran) can be used if patient cannot tolerate or absorb oral iron

Plummer-Vinson Syndrome Triad
- Dysphagia (esophageal)
- Glossitis
- Iron deficiency anemia
• monitoring response
  ▪ reticulocyte count will begin to increase after one wk
  ▪ Hb normalizes by 10 g/L per wk (if no blood loss)
  ▪ iron supplementation required for 4-6 mo to replenish stores

### Anemia of Chronic Inflammation

**Etiology**
- infection, malignancy, inflammatory and rheumatologic disease, chronic renal and liver disease, endocrine disorders (e.g. DM, hypothyroidism, hypogonadism, hypopituitarism)

**Pathophysiology**
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  ▪ enterocyte trapping of iron → increased hepcidin inhibits ferroportin (↓ iron into circulation)
  ▪ macrophage trapping of iron → reduced plasma iron levels making iron relatively unavailable for new hemoglobin synthesis
  ▪ marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present
- RBC survival is modestly decreased

**Investigations**
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen)
- "classic" serum iron indices (see Table 11)
  ▪ serum iron and TIBC low, % saturation normal
  ▪ serum ferritin is normal or increased
- anemia of chronic inflammation often co-exists with iron deficiency
- peripheral blood
  ▪ mild: usually normocytic and normochromic
  ▪ moderate: may be microcytic and normochromic
  ▪ severe: may be microcytic and hypochromic
- absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
- bone marrow
  ▪ normal or increased iron stores
  ▪ decreased or absent staining for iron in erythroid precursors

**Treatment**
- treat underlying disease
- only treat anemia in patients who can benefit from a higher hemoglobin
- IV iron if no benefit from PO iron
- erythropoietin indicated in chronic renal failure; not to be used if patient has concomitant curative solid tumor malignancy; ensure Hb target <110 g/L

### Sideroblastic Anemia

- uncommon compared to iron deficiency anemia or anemia of chronic inflammation

**Sideroblasts**
- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
- "normal": granules are small, randomly spread in the cytoplasm
  ▪ found in healthy individuals
- "ring": iron deposits in mitochondria, forming a ring around the nucleus
  ▪ abnormal, large granules
  ▪ the hallmark of sideroblastic anemia

**Etiology**
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  ▪ refractory anemia with ringed sideroblasts: a subtype of MDS (see Myelodysplastic Syndromes, H38)
  ▪ may be a preleukemic phenomenon (10% transform to AML)
- reversible
  ▪ drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, hypothyroidism
Clinical Features
- anemia symptoms (see Anemia, H6)
- hepatosplenomegaly, Fe⁺⁺ overload syndrome

Investigations
- serum iron indices
  - increased serum Fe⁺⁺, normal TIBC, increased ferritin, increased sTfR
- blood film/bone marrow biopsy
  - ringed sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikilocytosis, basophilic stippling

Treatment
- depends on etiology
  - X-linked: high dose pyridoxine (vitamin B6) in some cases
  - acquired: EPO and G-CSF
  - reversible: remove precipitating cause
- supportive transfusions for severe anemia

Lead Poisoning

Definition/Etiology
- blood lead levels greater than 80 µg/dL, possible symptomatology at 50 µg/dL.

Clinical Features
- identify source: consider occupational history, exposures history
- abdominal pain, constipation, irritability, difficulty concentrating

Treatment
- chelation therapy: dimercaprol and EDTA are first line agents

Thalassemia

- see Hemolytic Anemia – Thalassemia, H19

Normocytic Anemia

- MCV 80-100 fl.
- see Figure 2, Approach to Anemia, H6

Aplastic Anemia

Definition
- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

Epidemiology
- occurs at any age
- slightly more common in males

Etiology

Table 12. Etiology of Aplastic Anemia

<table>
<thead>
<tr>
<th>Congenital</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fanconi's anemia</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>Often T-cell mediated</td>
</tr>
<tr>
<td>Drugs</td>
<td>Idiosyncratic (i.e. chemotherapeutics)</td>
</tr>
<tr>
<td>Dose-related (i.e. chemotherapeutics)</td>
<td>Idiosyncratic (chloramphenicol, phenylbutazone)</td>
</tr>
<tr>
<td>Toxins</td>
<td>Benzene/organic solvents</td>
</tr>
<tr>
<td>DDT, insecticides</td>
<td>Ionizing Radiation</td>
</tr>
<tr>
<td></td>
<td>Post-Viral Infection</td>
</tr>
<tr>
<td></td>
<td>Parovirus B19, EBV, HDV, HEV, HBV, HHV6, HIV</td>
</tr>
<tr>
<td></td>
<td>Autoimmune (rare)</td>
</tr>
<tr>
<td></td>
<td>SLE, Graft-versus-host disease</td>
</tr>
<tr>
<td></td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>PIH, pregnancy, anorexia nervosa, thymoma</td>
</tr>
</tbody>
</table>

Clinical Features
- can present acutely or insidiously
- symptoms of anemia (see Anemia, H6), thrombocytopenia (see Thrombocytopenia, H7), and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)
Investigations

- exclude other causes of pancytopenia (Figure 4)
- CBC
  - anemia or neutropenia or thrombocytopenia (any combination) ± pancytopenia
  - decreased reticulocytes (<1% of the total RBC count)
- blood film
  - decreased number of normal RBCs
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement
  - decreased cellularity

Treatment

- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
  - judicious use so as to not increase the risk of immune sensitization to blood products
- immunosuppression
  - anti-thymocyte globulin: 50-60% of patients respond
  - cyclosporine
- allogenic bone marrow transplant
- growth factors: e.g. Eltrombopag (TPO receptor agonist)

Hemolytic Anemia

- uncommon cause for anemia (<5% of cases) with many etiologies (>200)

Classification

- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
  - immune
    - autoimmune: warm vs. cold autoimmune hemolytic anemias (AIHA), see Table 15 Classification of AIHA, H22
    - alloimmune: hemolytic disease of the fetus/newborn
  - non-immune
    - MAHA: thrombus in blood vessels causes RBCs to be sheared
    - other causes: PNH, hypersplenism, Thrombocytopenia purpura (exertional hemolysis), infection (e.g. malaria), snake venoms, mechanical heart valves

- also classified as intravascular or extravascular
  - intravascular: G6PD deficiency, TTP, DIC, and PNH
  - extravascular: AIHA and hereditary spherocytosis

Clinical Features Specific to HA

- jaundice
- dark urine (hemoglobinuria, bilirubin)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

Table 13. Investigations for Hemolytic Anemia

<table>
<thead>
<tr>
<th>Screening Tests</th>
<th>Tests Specific For Intravascular Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased LDH</td>
<td>Schistocytes on blood film</td>
</tr>
<tr>
<td>Decreased haptoglobin</td>
<td>Free hemoglobin in serum</td>
</tr>
<tr>
<td>Increased unconjugated bilirubin</td>
<td>Methemalbuminemia (heme + albumin)</td>
</tr>
<tr>
<td>Increased urobilinogen</td>
<td>Hemoglobinuria (immediate)</td>
</tr>
<tr>
<td>Reticulocytosis</td>
<td>Hamoglobinuria (delayed)</td>
</tr>
<tr>
<td></td>
<td>Plasma hemoglobin</td>
</tr>
</tbody>
</table>

Tests Specific for Extravascular Hemolysis

- Direct Coombs test (direct antiglobulin test)
  - Detects IgG or complement on the surface of RBC
  - Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination
  - Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction

- Indirect Coombs test (indirect antiglobulin test)
  - Detects antibodies in serum that can recognize antigens on RBCs
  - Mix patient's serum + donor RBCs + Coombs serum (anti-human Ig Ab); positive if agglutination
  - Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA
**Thalassemia**

**Definition**
- defects in production of the α or β chains of hemoglobin
  - resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
- clinical manifestations and treatment depends on specific gene and number of alleles affected
- common features
  - increasing severity with increasing number of alleles involved
  - hypochromic microcytic anemia
  - basophilic stippling, abnormally shaped RBCs on blood film

**Pathophysiology**
- defect may be in any of the Hb genes
  - normally 4 α genes in total; 2 on each copy of chromosome 16
  - normally 2 β genes in total; 1 on each copy of chromosome 11
  - fetal hemoglobin, HbF (α2γ2), switches to adult forms HbA (α2β2) and HbA2 (α2δ2) at 3-6 mo of life
  - HbA constitutes 97% of adult hemoglobin
  - HbA2 constitutes 3% of adult hemoglobin

**β-Thalassemia Minor (Thalassemia Trait)**

**Definition**
- defect in single allele of β gene (heterozygous)
- common in people of Mediterranean and Asian descent

**Clinical Features**
- None; a palpable spleen is very rare

**Investigations**
- Hb 100-140 g/L or 9-14 g/dL, MCV<70, normal Fe, normal RBC count
- peripheral blood film – microcytosis basophilic stippling
- Hb electrophoresis
  - specific: HbA2 increased to 3.5-5% (normal 1.5-3.5%)
  - non-specific: 50% have slight increase in HbF

**Treatment**
- no treatment required
- genetic counseling for patient and family

**β-Thalassemia Major**

**Definition**
- defect in both alleles of β gene (homozygous, autosomal recessive)

**Pathophysiology**
- ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs, and increase in HbF

**Clinical Features**
- initial presentation at age 6-12 mo when HbA normally replaces HbF
  - severe anemia, jaundice
  - iron overload
  - secondary to repeated transfusions and ineffective erythropoiesis
  - leads to iron-induced organ damage (liver, spleen, anterior pituitary, pancreas, and heart affected)
  - stunted growth and development (hypogonadal dwarf)
  - gross hepatosplenomegaly (due to extramedullary hematopoiesis)
  - radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumors)
  - skull x-ray has “hair-on-end” appearance
  - pathologic fractures common
- evidence of increased Hb catabolism (e.g. pigmented gallstones)
• death can result from
  ▪ untreated anemia (should transfuse)
  ▪ infection (should identify and treat early)
  ▪ iron overload: late complication secondary to repeated transfusions and ineffective
erthropoiesis

Investigations
• CBC: Hb 4-6 g/dL
• Hb electrophoresis
  ▪ HbA: 0-10% (normal >95%)
  ▪ HbA₂ >2.5%
  ▪ HbF: 90-100%

Treatment
• lifelong regular transfusions to suppress endogenous erythropoiesis
• iron chelation (e.g. deferoxamine, deferasirox, deferiprone) to prevent iron overload in organs
  and the formation of free radicals (which promote tissue damage and fibrosis)
• folic acid supplementation if not transfused
• allogenic bone marrow transplantation
• splenectomy (now performed less frequently)

β-Thalassemia Intermedia

Definition
• clinical diagnosis in patients whose clinical manifestations are too mild to be classified as
  thalassemia major, but too severe to be classified as thalassemia minor

Clinical Features
• wide variety of clinical phenotypes
• in most cases of TI, both β-globin genes affected
• three main mechanisms account for the milder phenotype compared to thalassemia major:
  (1) subnormal (vs. absent) beta-chain synthesis, (2) increased number of gamma chains, (3)
  coinheritance of alpha thalassemia
• complications more commonly seen in TI than thalassemia major include extramedullary
  hematopoiesis, leg ulcers, gallstones, thrombosis, and pulmonary HTN

α-Thalassemia

Definition
• defect(s) in α genes
• similar geographic distribution as β-thalassemia, but higher frequency among Asians and
  Africans

Clinical Features
• 1 defective α gene (aa/a-): clinically silent; normal Hb, normal MCV
• 2 defective α genes (cis: aa/– or trans: a-/a-): decreased MCV, normal Hb
  ▪ N.B. cis 2-gene deletion more common in Asia vs. trans 2-gene deletion more common in
    Africa – this leads to increased risk of fetal hydrops in offspring of Asian patients vs. African
    patients
• 3 defective α genes (a-/–): HbH (β4) disease; presents in adults, decreased MCV, decreased Hb,
splenomegaly
• 4 defective α genes (–/–): Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

Investigations
• peripheral blood film – screen for HbH inclusion bodies with special stain
• Hb electrophoresis not diagnostic for α-thalassemia
• DNA analysis using α gene probes is the only way to confirm the diagnosis
• referral to genetic counselor prior to childbearing for patients with 2-gene cis deletion (or
  3-gene deletion), due to risk of fetal hydrops if partner also carries thalassemia trait

Treatment
• depends on degree of anemia
  ▪ 1 or 2 defective α genes: no treatment required
  ▪ HbH disease: similar to β-thalassemia intermedia
  ▪ HbBarts: intrauterine transfusion
Sickle Cell Disease

- see Pediatrics, P48

Definition
- sickling disorders arise due to a mutant β-globin chain, most commonly caused by a Glu → Val substitution at position 6 (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb)
  - increased incidence of HbS allele with African or Mediterranean heritage (thought to be protective against malaria)
  - sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) – most commonly HbS-β-thal and HbSC disease

Pathophysiology
- at low pO2, deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes → ‘sickles’
- the pO2 level at which sickling occurs is related to the percentage of HbS present
  - heterozygotes (HbAS); sickling occurs at a pO2 of 40 mmHg
  - homozygotes (HbSS); sickling occurs at a pO2 of 80 mmHg
- sickling aggravated by acidemia, increased CO2, increased 2,3-DPG, fever, and osmolality
- fragile sickle cells then cause injury in two main ways:
  1. fragile sickle cells hemolyze (nitric oxide depletion)
  2. they also occlude small vessels (ischemia-reperfusion injury)

Clinical Features
- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection
  - increased risk of renal medullary carcinoma
- SCD-SS (HbSS)
  - chronic hemolytic anemia
  - jaundice in the first year of life
  - retarded growth and development ± skeletal changes
  - splenomegaly in childhood; splenic atrophy in adulthood
- SCD-SC often presents with acute pain episode
  1. aplastic crises
     - toxins and infections (especially parvovirus B19) transiently suppress bone marrow
  2. splenic sequestration crises
     - usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock
     - uncommon in adults due to asplenia from repeated infarction
  3. vaso-occlusive crises (infarction)
     - may affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen, and extremities), fever, and leukocytosis
     - precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses, and alcohol
  4. acute chest syndrome (see sidebar)
- SCD-SC (most common compound heterozygote)
  - 1:833 live births in African-Americans, common in West Africa
  - milder anemia than HbSS
  - similar complications as HbSS although typically milder and less frequent (exception is proliferative sickle retinopathy, glomerulonephritis, and avascular necrosis)
  - spleen not always atrophic in adults

Investigations
- sickle cell prep (detects sickling of RBCs under the microscope in response to O2 lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC, and other variants

<table>
<thead>
<tr>
<th>Table 14. Investigations for Sickle Cell Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbAS</strong></td>
</tr>
<tr>
<td>CBC</td>
</tr>
<tr>
<td>Peripheral Blood</td>
</tr>
<tr>
<td>Hb Electrophoresis</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Treatment
- genetic counseling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
• HbSS
  1. folic acid to prevent folate deficiency
  2. hydroxyurea to enhance production of HbF
     • mechanism of action: stops repression of Hb-γ chains and/or initiates differentiation of stem cells in which this gene is active
     • presence of HbF in the SS cells decreases polymerization and precipitation of HbS
  3. treatment of vaso-occlusive crisis
     • oxygen
     • hydration (reduces viscosity)
     • correct acidosis
     • analgesics/opiates
  • indication for exchange transfusion: acute chest syndrome, stroke, multi-organ failure, ICU admission
  • less routinely: antimicrobials for suspected infection
  4. prevention of crises
     • establish diagnosis
     • avoid conditions that promote sickling (hypoxia, acidosis, dehydration, fever)
     • vaccination in childhood (pneumococcus, meningococcus, H. influenzae b)
     • prophylactic penicillin (start age 3 mo and continue until at least 5 yr then continue on case by case basis)
     • good hygiene, nutrition, and social support
  5. screen for complications
     • regular blood work (CBC, reticulocytes, iron indices, BUN, LFTs, creatinine)
     • urinalysis annually (proteinuria, glomerulopathy)
     • transcranial doppler annually until 16 yr old (stroke prevention)
     • retinal examinations annually from 8 yr old (screen for retinopathy)
     • echocardiography starting at 10 yr old (screen for pulmonary HTN)

Table 15. Classification of AIHA

<table>
<thead>
<tr>
<th>Warm</th>
<th>Cold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibody Allotype</td>
<td>IgG</td>
</tr>
<tr>
<td>Agglutination Temperature</td>
<td>37ºC</td>
</tr>
<tr>
<td>Direct Coombs Test (direct anti-globulin test)</td>
<td>Positive for IgG ± complement</td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic Secondary to lymphoproliferative disorder (e.g. CLL, Hodgkin lymphoma) Secondary to autoimmune disease (e.g. SLE) Drug-induced (e.g. penicillin, quinine, methylprednisolone)</td>
</tr>
<tr>
<td>Blood Film</td>
<td>Spherocytes</td>
</tr>
<tr>
<td>Management</td>
<td>Treat underlying cause Corticosteroids Immunosuppression Splenectomy Folic acid</td>
</tr>
</tbody>
</table>

Autoimmune Hemolytic Anemia

Microangiopathic Hemolytic Anemia

Definition
• hemolytic anemia due to intravascular fragmentation of RBCs

Etiology
• see Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome, H30
• see Disseminated Intravascular Coagulation, H32
• eclampsia, HELLP syndrome, AFLP (see Obstetrics, OB17)
• malignant HTN
• vasculitis
• malfunctioning heart valves
• metastatic carcinoma
• drugs (calcineurin inhibitors, quinine, simvastatin)
• infections (severe CMV or meningococcus)
• catastrophic antiphospholipid antibody syndrome
Investigations
- blood film: evidence of hemolysis, schistocytes
- hemolytic workup
- urine: hemosiderinuria, hemoglobinuria

**Hereditary Spherocytosis**

- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
  - spleen makes defective RBCs more spherocytotic (and more fragile) by membrane removal; also acts as site of RBC destruction
- autosomal dominant with variable penetrance

Investigations
- blood film shows spherocytes, increased osmotic fragility, molecular analysis for spectrin gene

Treatment
- in severe cases, splenectomy + vaccination against pneumococcus, meningococcus, and *H. influenzae* b (avoid in early childhood)

**Hereditary Elliptocytosis**

**Definition/Etiology**
- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

Treatment
- immunizations; splenectomy for severe hemolysis

**Glucose-6-Phosphate Dehydrogenase Deficiency**

**Definition**
- deficiency in glucose-6-phosphate dehydrogenase (G6PD) leads to RBC sensitivity to oxidative stress due to a lack of reduced glutathione (GSH)

**Pathophysiology**
- X-linked recessive, prevalent in individuals of African, Asian, and Mediterranean descent

**Clinical Features**
- frequently presents as episodic hemolysis precipitated by
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

**Investigations**
- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
  - may have features of intravascular hemolysis (e.g. RBC fragments)

**Treatment**
- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases
Macrocytic Anemia

- MCV >100 fL
- see Figure 2, Approach to Anemia, H6

Table 16. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia

<table>
<thead>
<tr>
<th></th>
<th>Megaloblastic</th>
<th>Non-Megaloblastic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td>Large, oval, nucleated RBC precursor</td>
<td>Large round RBC</td>
</tr>
<tr>
<td></td>
<td>Hypersegmented neutrophils</td>
<td>Normal neutrophils</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Failure of DNA synthesis resulting in asynchronous maturation of RBC nucleus and cytoplasm</td>
<td>Reflects membrane abnormality with abnormal cholesterol metabolism</td>
</tr>
</tbody>
</table>

Vitamin B12 Deficiency

B12 (cobalamin) see Gastroenterology, G17 and Family Medicine – Nutrition, FM6
- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

Etiology

Table 17. Etiology of Vitamin B12 Deficiency

<table>
<thead>
<tr>
<th>Diet</th>
<th>Gastric</th>
<th>Intestinal Absorption</th>
<th>Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict vegan</td>
<td>Mucosal atrophy</td>
<td>Malabsorption</td>
<td>Transcobalamin II deficiency</td>
</tr>
<tr>
<td>More likely to present in pediatric population</td>
<td>Gastritis, autoimmune</td>
<td>Crohn's, celiac sprue, pancreatic insufficiency</td>
<td></td>
</tr>
<tr>
<td>Vegetarian in pregnancy</td>
<td>Pernicious anemia (see below)</td>
<td>Stagnant bowel</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Post-gastrectomy</td>
<td>Blind loop, stricture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fish tapeworm</td>
<td>Resection of ileum</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neomycin, biguanides, PPI, N2O anesthesia</td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology of Pernicious Anemia

- auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize B12 as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of B12
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- F:M = 1.6:1; often >60 yr old

Clinical Features

- neurological
  - cerebral (common, reversible with B12 therapy)
  - confusion, delirium, dementia
  - cranial nerves (rare)
  - optic atrophy
  - cord (irreversible damage)
    - posterior columns: decreased vibration sense, proprioception, and 2-point discrimination
    - pyramidal tracts: spastic weakness, hyperactive reflexes
  - peripheral neuropathy (variable reversibility)
  - usually symmetrical, affecting lower limbs more than upper limbs

Investigations

- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
- MCV >110 fL
- low reticulocyte count relative to the degree of anemia (<2%)
- serum B12 and RBC folate
  - caution: low serum B12 leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B12
  - alternatively, can measure urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils

Table 16. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Follow-up</th>
<th>Primary Outcome</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schilling et al.</td>
<td>One study evaluated 1,000 μg of oral B12 compared to 1,000 μg IM B12 on the same dosing schedule. The other compared 2,000 μg daily oral B12 to 1,000 μg IM B12 on a less frequent dosing schedule. Neurological and hematomasal end points were evaluated.</td>
<td>90-94 mo.</td>
<td>No significant difference was observed between groups in either study.</td>
<td>No significant difference was observed between groups in either study.</td>
</tr>
</tbody>
</table>

Results: Meta-analysis was not attempted due to study heterogeneity. Both studies reported improvements in hematomasal and neurological end-points in both oral and IM groups. No significant difference was observed between groups in either study. Conclusions: Limited data suggesting high dose oral vitamin B12 (1,000-2,000 μg) is equivalent to IM vitamin B12 on the same or less frequent dosing schedule. This data is severely limited by small sample sizes and short follow-up periods. Insufficient numbers of patients with malabsorption conditions were included to generalize these results to the entire primary care population.
• bone marrow
  ▪ hypercellularity
  ▪ nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from
    the development of the cytoplasm)
  ▪ bilirubin and LDH
  ▪ elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
  ▪ Schilling test (see sidebar H24) to distinguish pernicious anemia from other causes
    ▪ anti-intrinsic factor antibody, anti-parietal cell antibody

Treatment
• vitamin B₁₂ 1,000 µg IM monthly for life or 1,000-1,200 µg PO daily if intestinal absorption intact
• less frequent, higher doses may be as effective (e.g. 1,000 µg IM q3mo)
• watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

Folate Deficiency

• uncommon in developed countries due to extensive dietary supplementation
• folate stores are depleted in 3-6 mo
• folate commonly found in green, leafy vegetables and fortified cereals

Etiology

Table 18. Etiology of Folate Deficiency

<table>
<thead>
<tr>
<th>Diet/Deficiency</th>
<th>Malabsorption</th>
<th>Drugs</th>
<th>Increased Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td>Celiac sprue</td>
<td>Anti-folates (methotrexate)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>IBD</td>
<td>Anticonvulsants (phenytoin)</td>
<td>Hemolytic</td>
</tr>
<tr>
<td>Elderly/infants</td>
<td>Infiltrative bowel disease</td>
<td>Alcohol</td>
<td>Prematurity</td>
</tr>
<tr>
<td>Poor intake</td>
<td>Short bowel syndrome</td>
<td>Oral contraceptive</td>
<td>Exfoliative dermatitis/psoriasis</td>
</tr>
</tbody>
</table>

Clinical Features
• mild jaundice due to hemolysis of RBCs secondary to ineffective hemoglobin synthesis
• glossitis and angular stomatitis
• melanin pigmentation (rare)
• purpura secondary to thrombocytopenia (rare)
• unlike B₁₂ deficiency, folate deficiency has no neurologic manifestations

Investigations
• similar to B₁₂ deficiency (CBC, reticulocytes, blood film, RBC folate, serum B₁₂)
• if decreased RBC folate, rule out B₁₂ deficiency as cause

Management
• folic acid 1-5 mg PO OD x 1-4 mo; then 1 mg PO OD maintenance if cause is not reversible

Hemostasis

Three Phases of Hemostasis

1. Primary Hemostasis
• goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
• vessel injury results in collagen/subendothelial matrix exposure and release of
  vasoconstrictors
• blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 11a)
  ▪ adhesion: platelets adhere to subendothelium via von Willebrand factor (vWF)
  ▪ activation: platelets are activated resulting in change of shape and release of ADP and
    thromboxane A₂
  ▪ aggregation: these factors further recruit and aggregate more platelets resulting in formation
    of localized hemostatic plug

2. Secondary Hemostasis
• platelet plug is reinforced by production of fibrin clot in secondary hemostasis (Figure 11b)
• extrinsic pathway
  ▪ initiation of coagulation in vivo
• intrinsic pathway
  ▪ amplification once coagulation has started

3. Fibrin Stabilization and Fibrinolysis (resolution)
• conversion from soluble to insoluble clot
• once healing initiated, clot dissolution (anticoagulant pathway)
**Table 19. Commonly Used Tests of Hemostasis**

<table>
<thead>
<tr>
<th>Type of Hemostasis</th>
<th>Test</th>
<th>Reference Range</th>
<th>Purpose</th>
<th>Examples of Associated Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>Platelet count</td>
<td>150,000-400,000/mm³</td>
<td>To quantitate platelet number</td>
<td>Low in ITP, HUS/TTP, DIC</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>APTT</td>
<td>22-35 s</td>
<td>Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway</td>
<td>Prolonged in hemophilia A and B</td>
</tr>
<tr>
<td></td>
<td>Used to monitor heparin therapy and intrinsic pathway factors</td>
<td>Used to monitor heparin therapy and intrinsic pathway factors</td>
<td>N.B. High if antiphospholipid antibodies (i.e. lupus anticoagulant) are present</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PT</td>
<td>11-24 s</td>
<td>Measures extrinsic pathway (factor VII in particular) and common pathway</td>
<td>Prolonged in factor VII deficiency</td>
</tr>
<tr>
<td></td>
<td>INR</td>
<td>0.9-1.2</td>
<td>Only used to monitor warfarin therapy</td>
<td>Clotting factor(s) deficiency if test becomes normal</td>
</tr>
<tr>
<td></td>
<td>Mixing studies</td>
<td>Differentiate inhibitors of clotting factor(s) from a deficiency in clotting factor(s)</td>
<td>Inhibitors of clotting factor(s) if test still abnormal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Euglobulin lysis time</td>
<td>N &gt;90 min</td>
<td>Looks for accelerated fibrinolysis</td>
<td>May be accelerated in DIC or factor XIII deficiency</td>
</tr>
<tr>
<td><strong>Fibrinolysis</strong></td>
<td></td>
<td></td>
<td></td>
<td>Decreased in hereditary deficiency of fibrinogen</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Fibrogen</td>
<td>Fibrinogen degradation products (FDPs), D-dimers</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific factor assays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tests of physiological inhibitors (antithrombin, protein S, protein C, hereditary resistance to activated protein C [APC])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tests of pathologic inhibitors (e.g. lupus anticoagulant)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 20. Signs and Symptoms of Disorders of Hemostasis**

<table>
<thead>
<tr>
<th>Type of Hemostasis</th>
<th>Primary (Platelet)</th>
<th>Secondary (Coagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface Cuts</strong></td>
<td>Excessive, prolonged bleeding</td>
<td>Normal/slightly prolonged bleeding</td>
</tr>
<tr>
<td><strong>Onset After Injury</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Site of Bleeding</strong></td>
<td>Superficial i.e. mucosal (nasal, gingival, GI tract, uterine), skin</td>
<td>Deep i.e. joints, muscles, GI tract, GU tract</td>
</tr>
<tr>
<td><strong>Lesions</strong></td>
<td>Petechiae, ecchymoses</td>
<td>Hemarthroses, hematomas</td>
</tr>
</tbody>
</table>

**Figure 11a. Platelet activation cascade**

**Figure 11b. Coagulation cascade**

**Figure 12. Clotting factors involved in PT and PTT**
## Disorders of Primary Hemostasis

### Definition
- inability to form an adequate platelet plug due to:
  - disorders of blood vessels
  - disorders of platelets: abnormal function/numbers
  - disorders of vWF

### Classification

<table>
<thead>
<tr>
<th>Low platelet count:</th>
<th>Normal platelet count:</th>
<th>Hereditary</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia (see H6)</td>
<td>Platelet dysfunction</td>
<td>Osler-Weber-Rendu syndrome (GP Ib deficiency)</td>
<td>Purpura simplex (easy bruising)</td>
</tr>
<tr>
<td>Sequestration</td>
<td>Glanzmann syndrome (GP IIb/IIIa deficiency)</td>
<td>Connective tissue disorders</td>
<td>Senile purpura</td>
</tr>
<tr>
<td>Decreased production</td>
<td>Hereditary</td>
<td>Acquired</td>
<td>Uremia/CRF</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>(\text{CRF} = \text{chronic renal failure; HSP = Henoch-Schönlein purpura})</td>
<td>Drugs (ASA, EtOH, NSAIDs)</td>
<td>Myeloproliferative disorders</td>
</tr>
</tbody>
</table>

### Immune Thrombocytopenic Purpura

#### Table 22. Immune Thrombocytopenic Purpura

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Age</td>
<td>2-5 yr</td>
<td>20-40 yr</td>
</tr>
<tr>
<td>Gender</td>
<td>None</td>
<td>F&gt;M (3:1)</td>
</tr>
<tr>
<td>History of Recent Infection</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset of Bleed</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Duration</td>
<td>Usually weeks</td>
<td>Months to years</td>
</tr>
<tr>
<td>Spontaneous Remissions</td>
<td>80% or more</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

#### ACUTE (CHILD-TYPE) ITP
- see Pediatrics, P50

#### CHRONIC (ADULT-TYPE) ITP
- most common cause of isolated thrombocytopenia
- diagnosis of exclusion (i.e. isolated thrombocytopenia [platelets <100,000/mm³] and the absence of any obvious initiating and/or underlying cause)
Pathophysiology
- an acquired immune-mediated disorder with
  - anti-platelet antibodies bind to platelet surface → increased splenic destruction and clearance
  - impaired platelet production
  - helper T-cell and cytotoxic T-cell activation also implicated in platelet destruction

Clinical Presentation
- can present asymptomatic, minimal bruising, or serious bleed (GI bleed, skin and mucosal hemorrhage or intracranial hemorrhage), lethargy, fatigue

Investigations
- CBC and reticulocyte count: thrombocytopenia (request retic count if not an isolated thrombocytopenia)
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets (to rule out platelet clumping)
- HIV, HCV (if risk factors are present)
- bone marrow aspirate and biopsy: increased number of megakaryocytes
  - recommended in patients >60 yr of age, pre-splenectomy or have failed multiple lines of ITP treatment, those with systemic symptoms, an abnormal blood film, and/or abnormal signs to rule out other causes of thrombocytopenia (e.g. myelodysplasia)

Treatment
- rarely indicated if platelets >30,000/mm³ unless active bleeding, trauma, or surgery

A. Emergency Treatment (active bleeding (CNS, GI, or GU) or in need of emergency surgery)
  - general measures: stop drugs reducing platelet function, control blood pressure, minimize trauma
  - corticosteroids: prednisone (1 mg/kg) or methylprednisolone (1 g/d x 3 d) or dexamethasone (40 mg PO x 4 d)
  - antifibrinolytic: tranexamic acid (1 g PO tid or 1 g IV q6h) if refractory bleeding
  - IVIg 1 g/kg/d x 2 doses, or 2 g/kg over 5 d
  - platelet transfusion: for life-threatening bleeding
  - emergency splenectomy: may be considered, vaccinations prior (pneumococcus, meningococcus, *H. influenzae* b)
  - management of intracranial bleeding: IV steroids, IVIg, platelets, emergency splenectomy, and then craniotomy; maintain Plt >100,000/mm³ for at least 7 wk post intracranial hemorrhage

B. Non-Urgent Treatment (platelet count <20,000-30,000/mm³ and no bleeding OR platelet count <50,000/mm³ and significant bleeding symptoms)
  - platelet transfusion does not work
  - 1st Line
    - corticosteroids (dexamethasone 40 mg/d x 4 wk or prednisone 1 mg/kg/d)
    - IVlg
    - anti-D: appropriate for Rh+ non-splenectomized patients, but can cause hemolysis (avoid if low Hb at baseline or if DAT is positive) (warning label now attached to this medication regarding risk of intravascular hemolysis)
  - 2nd Line
    - splenectomy (need vaccinations prior to splenectomy: pneumococcus, meningococcus, *H. influenzae* b)
    - immunosuppressants (azathioprine, cyclophosphamide)
    - rituximab
    - danazol, vincristine
    - thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag)

Prognosis
- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- overall relatively benign, mortality 1-2%, (2x higher mortality than the unaffected population)
- major concern is cerebral hemorrhage at Plt <5,000/mm³, although very rare
Heparin-Induced Thrombocytopenia

- heparin-induced thrombocytopenia: immune-mediated reaction following treatment with heparin leading to coagulation activation
- heparin-associated thrombocytopenia: transient thrombocytopenia following administration of heparin

Table 23. Heparin-Induced Thrombocytopenia (HIT) (Previously Known as HIT Type II)

| Pathophysiology | Immune mediated  
| Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system |
| Diagnosis | 50% reduction in platelets while on heparin within 5-15 wk of initiation |
| Onset of Decreased Platelets | 5-15 wk (if previously exposed to heparin, HIT can develop in hours) |
| Risk of Thrombosis | ~30% (25% of events are arterial) |
| Clinical Features | Bleeding complications uncommon  
| Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis  
| Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney)  
| Heparin-induced skin necrosis (with LMWH)  
| Acute platelet activation syndromes: acute inflammatory reactions (e.g., fever/chills, flushing, etc.)  
| Transient global amnesia (rare) |
| Specific Tests | Pre-test clinical scoring models can help rule-out HIT: 4-Ts (see Table 24) and the HIT Expert Probability (HEP) score  
| 14C serotonin release assay (uses donor platelets with 14C serotonin and heparin with patient’s plasma)  
| ELISA for HIT-Ig (more sensitive, less specific than serotonin assay)  
| Ultrasound of lower limb veins for DVT |
| Management | Clinical suspicion of HIT should prompt discontinuation of heparin and LWMH (specific tests take several days)  
| Initiate anticoagulation with a non-heparin anticoagulant  
| e.g. argatroban, danaparoid, fondaparinux, bivalirudin unless there is a strong contraindication (duration of treatment at least 2-3 mo if no thrombotic event, and at least 3-6 mo if thrombotic event has occurred)  
| Warfarin should only be restarted when platelet count >100 x 10^9/L  
| Allergy band and alert in patient records |

Table 24. The 4-T Pre-Test Clinical Scoring Model for HIT

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thrombocytopenia</td>
<td>Platelet count fall &gt;50% AND platelet nadir &gt;20 x 10^9/L</td>
<td>Platelet count fall 30-50% OR platelet nadir 10-90 x 10^9/L</td>
<td>Platelet count fall &lt;30% OR platelet nadir &lt;10 x 10^9/L</td>
</tr>
<tr>
<td>2. Timing of Platelet Count Fall</td>
<td>Clear onset between days 5-10 of heparin exposure OR platelet count fall at ≤1 d if prior heparin exposure within last 30 d</td>
<td>Consistent with fall in platelet count at 5-10 d but unclear (e.g., missing platelet counts) OR onset after day 10 OR fall ≤1 d with prior heparin exposure within 30-100 d</td>
<td>Platelet count fall &lt;4 d of heparin exposure, and no recent heparin</td>
</tr>
<tr>
<td>3. Thrombosis or Other Sequelae</td>
<td>Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus</td>
<td>Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven</td>
<td>None</td>
</tr>
<tr>
<td>4. Other Causes for Thrombocytopenia</td>
<td>None apparent</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

6-8 points = high probability of HIT; 4-5 points = intermediate probability of HIT; 0-3 points = low probability of HIT

J Thromb Haemost 2008;6:159-165
Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Table 25. TTP and HUS

<table>
<thead>
<tr>
<th>TTP</th>
<th>HUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Predominantly adult</td>
</tr>
<tr>
<td>Etiology</td>
<td>Deficiency of metalloproteinase that breaks down ultra-large vWF multimers</td>
</tr>
<tr>
<td></td>
<td>• Congenital (genetic absence of ADAMTS-13)</td>
</tr>
<tr>
<td></td>
<td>• Acquired (drugs, malignancy, transplant, HIV-associated, idiopathic)</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>1. Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>2. MAHA</td>
</tr>
<tr>
<td></td>
<td>4. Renal failure</td>
</tr>
<tr>
<td></td>
<td>5. Fever</td>
</tr>
<tr>
<td>Investigations (both TTP, HUS)</td>
<td>CBC and blood film: decreased platelets and schistocytes</td>
</tr>
<tr>
<td></td>
<td>PT, aPTT, fibrinogen: normal</td>
</tr>
<tr>
<td></td>
<td>Markers of hemolysis: increased unconjugated bilirubin, increased LDH, decreased haptoglobin</td>
</tr>
<tr>
<td></td>
<td>Negative Coombs test</td>
</tr>
<tr>
<td></td>
<td>Creatinine, urea, to follow renal function</td>
</tr>
<tr>
<td></td>
<td>Stool C&amp;S (HUS)</td>
</tr>
<tr>
<td>Management (both TTP, HUS)</td>
<td>Medical emergency</td>
</tr>
<tr>
<td></td>
<td>Plasmapheresis ± steroids</td>
</tr>
<tr>
<td></td>
<td>Platelet transfusion is contraindicated (increased microvascular thrombosis)</td>
</tr>
<tr>
<td></td>
<td>Plasma infusion if plasmapheresis is not immediately available</td>
</tr>
<tr>
<td></td>
<td>TTP mortality ~90% if untreated</td>
</tr>
</tbody>
</table>

von Willebrand Disease

Pathophysiology
- heterogeneous group of defects, usually mild in severity
- usually autosomal dominant (type 3 is autosomal recessive)
- qualitative or quantitative abnormality of vWF
  - vWF needed for platelet adhesion and acts as carrier for Factor VIII; abnormality of vWF can affect both primary and secondary hemostasis
  - vWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion, both large and small multimers complex with Factor VIII

Classification
- type 1: mild quantitative defect (decreased amount of vWF and proportional decrease in vWF activity) – 75% of cases
- type 2: qualitative defect (vWF activity disproportionally lower than quantity) – 20-25% of cases
- type 3: severe total quantitative defective (no vWF produced) – rare

Clinical Features
- mild
  - asymptomatic
  - mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia
- moderate to severe
  - as above but more severe, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

Investigations

Table 26. Investigations in vWD

<table>
<thead>
<tr>
<th>Test</th>
<th>Expected Result</th>
<th>Test</th>
<th>Expected Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT</td>
<td>N/↑</td>
<td>von Willebrand antigen</td>
<td>↓</td>
</tr>
<tr>
<td>Factor VII</td>
<td>N/↓</td>
<td>Blood group</td>
<td>Affects antigen quantification (↓ in group D)</td>
</tr>
<tr>
<td>Pt Count</td>
<td>N/↓</td>
<td>vWF multimer analysis</td>
<td>Multimer variants</td>
</tr>
<tr>
<td>Ristocetin Activity</td>
<td>↓ (cofactor for vWF-Pt binding)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hematology Disorders of Prim. Hemostasis/Disorders of Secondary Hemostasis

Treatment

- desmopressin (DDAVP) is treatment of choice for type 1 vWD
  - causes release of vWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs
  - need good response before using with further bleeding
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron, antifibrinolytic) to stabilize clot formation
- high-purity Factor VIII concentrate containing vWF (Hemate P) in select cases and type
  - frozen plasma (FP) is not useful
  - need to monitor vWF and factor VIII levels (very high factor VIII level can cause thrombosis)
- conjugated estrogens (increase vWF levels)

Prognosis

- may fluctuate, often improves during pregnancy, inflammation, and with age

Disorders of Secondary Hemostasis

Definition

- inability to form an adequate fibrin clot
  - disorders of clotting factors or co-factors
  - disorders of proteins associated with fibrinolysis
- characterized by delayed bleeding, deep muscular bleeding, spontaneous joint bleeding

Table 27. Classification of Secondary Hemostasis Disorders

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII: Hemophilia A, vWD</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Factor IX: Hemophilia B (Christmas Disease)</td>
<td>DIC</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Vitamin K deficiency</td>
</tr>
<tr>
<td>Other factor deficiencies are rare</td>
<td>Acquired inhibitors</td>
</tr>
</tbody>
</table>

Hemophilia A (Factor VIII Deficiency)

Pathophysiology

- X-linked recessive, 1/5,000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

Clinical Features

- see Table 20 – Signs and Symptoms of Disorders of Hemostasis, H26
- older patients may also have HIV or HCV from contaminated blood products

Investigations

- prolonged aPTT, normal INR (PT)
- decreased Factor VIII (<40% of normal)
- vWF usually normal or increased

Treatment

- desmopressin (DDAVP) in mild hemophilia A
- recombinant Factor VIII concentrate for
  - prophylaxis (2-3x/wk at home)
  - minor but not trivial bleeding (e.g. hemarthroses)
  - major potentially life-threatening bleeding (e.g. multiple trauma)
  - anti-fibrinolytic agents (e.g. tranexamic acid)

Hemophilia B (Factor IX Deficiency)

- i.e. Christmas disease
- X-linked recessive, 1/30,000 males
- clinical and laboratory features identical to hemophilia A (except decreased Factor IX)
- treatment: recombinant Factor IX concentrate, anti-fibrinolytic agents

Factor XI Deficiency

- i.e. Rosenthal syndrome
- autosomal recessive; more common in Ashkenazi Jewish population
- usually mild, often diagnosed in adulthood
- Factor XI level does not correlate with bleeding risk
- treatment: frozen plasma, Factor XI concentrate
Liver Disease

- see Gastroenterology, G28

Pathophysiology
- deficient synthesis of all factors except VIII (also made in endothelium and in acute phase response)
- aberrant synthesis of fibrinogen
- deficient clearance of hemostatic ‘debris’ and fibrinolytic activators
- accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
- miscellaneous: inhibition of secondary hemostasis by FDPs

Investigations
- peripheral blood film: target cells
- primary hemostasis affected
  - thrombocytopenia 2o to hypersplenism, folate deficiency, alcohol intoxication, DIC, decreased production of thrombopoietin
  - platelet dysfunction (e.g. alcohol abuse)
- secondary hemostasis affected
  - elevated INR (PT), aPTT and TT, low fibrinogen in end-stage liver disease

Treatment
- supportive, treat liver disease, blood products if active bleeding (frozen plasma, platelets, cryoprecipitate)

Vitamin K Deficiency

Etiology
- drugs
  - oral anticoagulants which inhibit Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease (decreased stores)
- malabsorption (e.g. celiac disease)
- hemorrhagic disease of newborn, see Pediatrics, P70

Investigations
- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX, X (vitamin K-dependent)

Treatment
- hold anticoagulant
- vitamin K 1 mg PO for INR between 4.5 and 10 and no active bleeding (excludes hemorrhagic disease of the newborn)
- if bleeding, give vitamin K 10 mg IV
- if life-threatening bleeding and vitamin K antagonist use, give frozen plasma or prothrombin complex concentrate (PCC)
- PCCs are contraindicated if there is a previous history of HIT
- use FFP if PCC is contraindicated or unavailable
- note: excessive vitamin K will delay therapeutic warfarin anticoagulation once re-started

Disseminated Intravascular Coagulation

- see Obstetrics, OB20

Definition
- uncontrolled release of plasmin and thrombin leading to intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage

Etiology
- occurs as a complication of many other conditions
- widespread endothelial damage ± extensive inflammatory cytokine release
### Table 28. Etiology of DIC

<table>
<thead>
<tr>
<th>Activation of Procoagulant Activity</th>
<th>Endothelial Injury</th>
<th>Reticuloendothelial Injury</th>
<th>Vascular Stasis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid antibody syndrome (APS)</td>
<td>Intraocular hemolysis</td>
<td>Incompatible blood, malaria</td>
<td>Liver disease</td>
<td>Hypothesis</td>
</tr>
<tr>
<td>Tissue injury</td>
<td>Intraocular hemolysis</td>
<td>Metastatic adenocarcinoma</td>
<td>Splenectomy</td>
<td>Hypothesis</td>
</tr>
<tr>
<td>Obstetric complications, trauma, burns,</td>
<td>Intraocular hemolysis</td>
<td>Aortic aneurysm</td>
<td>Hypothesis</td>
<td>Acute</td>
</tr>
<tr>
<td>malignancy</td>
<td>Tissue injury</td>
<td>Giant hemangioma</td>
<td>Hypothesis</td>
<td>hypoxia/</td>
</tr>
<tr>
<td>Snake venom, fat embolism, heat stroke</td>
<td></td>
<td></td>
<td></td>
<td>acidosis</td>
</tr>
</tbody>
</table>

### Clinical Features
- presence of both hemorrhage and clotting

### Table 29. Clinical Features of DIC

<table>
<thead>
<tr>
<th>Sign of Microvascular Thrombosis</th>
<th>Signs of Hemorrhagic Diathesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological: multifocal infarcts, delirium, coma, seizures</td>
<td>Bleeding from any site in the body (≥2 to decreased platelets and clotting factors)</td>
</tr>
<tr>
<td>Skin: focal ischemia, superficial gangrene</td>
<td>Neurologic: intracranial bleeding</td>
</tr>
<tr>
<td>Renal: oliguria, azotemia, cortical necrosis</td>
<td>Skin: petechiae, ecchymosis, oozing from puncture sites</td>
</tr>
<tr>
<td>Pulmonary: ARDS</td>
<td>Renal: hematuria</td>
</tr>
<tr>
<td>GI: acute ulceration</td>
<td>Mucosal: gingival oozing, epistaxis, massive bleeding</td>
</tr>
<tr>
<td>RBC: microangiopathic hemolysis</td>
<td></td>
</tr>
</tbody>
</table>

### Investigations
- primary hemoestasis: decreased platelets
- secondary hemoestasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
- fibrinolysis: increased FDPs or D-dimers, short euglobulin lysis time (i.e. accelerated fibrinolysis)
- extent of fibrin deposition: urine output, urea, RBC fragmentation

### Treatment
- recognize early and treat underlying disorder
- individualized critical care support
- in hemorrhage: replacement of hemostatic elements with platelet transfusion, frozen plasma, cryoprecipitate
  - maintain platelets >50,000/mm³ and hemoglobin >80 g/L
  - 4-5 units of FFP if INR >1.5 or aPTT >38
  - 10 units of cryoprecipitate if fibrinogen <100 mg/dL
  - 1 adult dose of buffy-coat platelets if <10,000 (<20,000 if febrile, <50,000 before invasive procedure)
- in thrombotic phase: UFH or LMWH in critically ill, non-bleeding patients

### Table 30. Screening Test Abnormalities in Coagulopathies

<table>
<thead>
<tr>
<th>Increased INR Only</th>
<th>Increased PTT Only</th>
<th>Both Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Hemophilia A and B</td>
<td>Prothrombin deficiency</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>vWD</td>
<td>Fibrinogen deficiency</td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td>Heparin</td>
<td>Factor V and X deficiency</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Antiphospholipid Ab</td>
<td>Severe liver disease</td>
</tr>
<tr>
<td>Factor VII inhibitors</td>
<td>Factor inhibitors</td>
<td>Factor X and XIII, prothrombin, and fibrinogen inhibitors</td>
</tr>
</tbody>
</table>

### Venous Thromboembolism

### Definition
- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- superficial thrombophlebitis, deep vein thrombosis (DVT), and pulmonary embolism (PE)
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- more common in lower extremity than upper extremity
- incidence ~1% if age >60 yr
- most important sequelae are pulmonary embolism (~50% chance with proximal DVT) and chronic venous insufficiency
Thromboembolism
- limits development of late complications, e.g., postphlebitic syndrome, chronic venous
- treatment of massive ileofemoral thrombosis with acute lower limb ischemia and/or venous
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
  - age (risk increases with age)
  - surgery (especially orthopedic, thoracic, GI, and GU)
  - trauma (especially fractures of spine, pelvis, femur or tibia, spinal cord injury)
  - neoplasms (especially lung, pancreas, colon, rectum, kidney, and prostate)
  - blood dyscrasias (myeloproliferative neoplasms, especially PV, ET), PNH, hyperviscosity
    (multiple myeloma, polycythemia, leukemia, sickle cell disease)
  - prolonged immobilization (CHF, stroke, MI, leg injury)
  - hormone related (pregnancy, OCP, HRT, SERMs)
  - APS
  - heart failure (risk of DVT greatest with right heart failure and peripheral edema)
- idiopathic (10-20% are later found to have cancer)

Clinical Features of DVT
- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth, and tenderness
- palpable cord (thrombosed vein)
- unilateral leg edema, erythema, warmth, and tenderness
- absence of physical findings does not rule out disease

Differential Diagnosis of DVT
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvular insufficiency,
- venography is the gold standard, but is expensive, invasive, and higher risk
- other non-invasive tests include MRI and impedance plethysmography

Inflammations for DVT
- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease and no other acute medical issues
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~ 95%
  - sensitivity for calf DVT ~ 70%
- other non-invasive tests include MRI and impedance plethysmography
- venography is the gold standard, but is expensive, invasive, and higher risk

Post-Thrombotic Syndrome
- development of chronic venous stasis signs and symptoms secondary to a deep venous thrombosis
- symptoms: pain, venous dilatation, edema, pigmentation, skin changes, venous ulcers
- clinical severity can be estimated based on the Villalta score
- large impact on quality of life following a DVT
- treatment: extremity elevation, exercise, continuous compression stockings, intermittent
  pneumatic compression therapy, skin/ulcer care
- for Clinical Features and Treatment of PE, see Respirology. R18

Approach to Treatment of Venous Thromboembolism

Purpose
- prevent further clot extension (3 mo duration is optimal)
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- treatment of massive ileofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications, e.g., postphlebitic syndrome, chronic venous
  insufficiency, and chronic thromboembolic pulmonary HTN

Absolute Contraindications to Treatment

<table>
<thead>
<tr>
<th>Absolute Contraindications to Treatment</th>
<th>Relative Contraindications to Treatment</th>
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</thead>
<tbody>
<tr>
<td>Active bleeding</td>
<td>Mild-moderate bleeding diathesis or thrombocytopenia</td>
</tr>
<tr>
<td>Severe bleeding diathesis or platelet count &lt; 20,000/mm³</td>
<td>Brain metastases</td>
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<tr>
<td>Intracranial bleeding</td>
<td>Recent major trauma</td>
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<tr>
<td>Neurosurgery or ocular surgery within 10 d</td>
<td>Recent stroke</td>
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<td>Major abdominal surgery within past 2 d</td>
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<td>GI/GU bleeding within 1-4 d</td>
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<td></td>
<td>Endocarditis</td>
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<tr>
<td></td>
<td>Severe HTN (sBP &gt; 200 or dBP &gt; 120)</td>
</tr>
</tbody>
</table>

Relative Contraindications to Treatment

- Paralysis, paresis, or recent orthopedic casting of lower extremity (1)
- Recent bedridden (> 3 d) or major surgery within past 4 wk (1)
- Localized tenderness in deep vein system (1)
- Swelling of entire leg (1)
- Calf swelling > 3 cm other than leg (measured 10 cm below the tibial tuberosity) (1)
- Pitting edema greater in the symptomatic leg (1)
- Collateral non-varicose superficial veins (1)
- Active cancer or cancer treated within 6 mo (1)
- Alternative diagnosis more likely than DVT (e.g., Baker’s cyst, cellulitis, muscle damage, superficial venous thrombosis) (1)

Total Score Interpretation
- Low: High probability, 1-2: Moderate probability, 3-8: Low probability

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- Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism
  - Coccarde SB Syst Rev 2009;300:1367
  - Study: Meta-analysis of 8 RCTs (2,994 patients)
  - comparing different durations of treatment with vitamin K antagonists in patients with symptomatic VTE
  - Results: In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.18, 95% CI 0.13-0.26). In addition, there was no observed excess of VTE recurrences following cessation of prolonged treatment (i.e., rebound phenomenon) (OR 1.24, 95% CI 0.9-1.38). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61, 95% CI 1.48-4.61).
  - Conclusion: Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.
Initial Treatment

- low molecular weight heparin (LMWH)
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; <1% HIT; safe and effective outpatient therapy
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis
  - renally cleared – must adjust dose in patients with renal dysfunction
- unfractionated heparin (UFH)
  - in patient with average risk of bleed; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- alternatives to LMWH and UFH
  - heparinoids (patients with HIT), direct thrombin inhibitors (hirudin, lepirudin, argatroban, dabigatran), Factor Xa inhibitors (fondaparinux, rivaroxaban)
  - thrombolytic drugs (e.g. streptokinase, tPA) reserved for acute limb/life-threatening thrombosis, and low bleeding risk

Long-Term Treatment

- warfarin
  - standard treatment; should be initiated with heparin overlap: dual therapy for at least 5 d, due to initial prothrombotic state, half life of vitamin K factors and risk of warfarin-induced skin necrosis
  - discontinue heparin after INR >2.0 for two consecutive days
  - warfarin should be dosed to maintain INR at 2-3 except in select cases
  - monitor INR twice weekly for 1-2 wk, then weekly until INR stable, then every 2-4 wk
  - LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients (see sidebar, H34)
  - duration of anticoagulant treatment (with warfarin unless otherwise noted)
    - first episode DVT with transient risk factor: 3 mo
    - first episode DVT with ongoing risk factor (e.g. cancer, antiphospholipid antibody) or >1 risk factor: consider indefinite therapy
    - first episode DVT with no identifiable risk factor (idiopathic) or single inherited risk factor (e.g. Factor V Leiden): 6-12 mo or indefinite therapy (controversial)
    - recurrent DVT (2 or more episodes): indefinite therapy
  - IVC filters
    - temporary filter indicated only if distal acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding)
    - must remove once safe to do so as filter is pro-thrombotic in the longterm (anticoagulation if left in)
  - special considerations
    - pregnancy: treat with LMWH during pregnancy, then warfarin for 4-6 wk post-partum (minimum total anticoagulation time of 3-6 mo)
    - surgery: avoid elective surgery in the first month after a venous or arterial thromboembolic event
      - pre-operatively: IV heparin may be used up to 6 h pre-operatively
      - perioperatively: surgery safe when INR <1.5; warfarin should be discontinued for at least 4 wk pre-operatively to allow INR to fall
      - post-operatively: IV heparin or LMWH can be used for anticoagulation (start 12 h after major surgery until therapeutic INR reached after restarting warfarin)
      - for patients at high risk for thromboembolism (VTE <12 wk, recurrent VTE, lupus anticoagulant, atrial fibrillation with prior stroke, mechanical heart valve), IV heparin or LMWH (bridging) should be given before and after the procedure while the INR is below 2.0

Prophylaxis

- see sidebar
- consider for those with a moderate to high risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), intermittent pneumatic compression (IPC)
- UFH 5,000 IU SC bid for moderate risk
- UFH 5,000 IU SC tid or LMWH as per hospital protocol (i.e. enoxaparin 40 mg SC daily) or UFH 5,000 IU SC tid for high risk

Contraindications and Adverse Reactions of Anticoagulant Therapy

- absolute: active bleeding, severe bleeding diathesis, or platelets <20 x 10^9/L (<20,000/mm^3), intracranial bleeding, neuro or ocular surgery within <10 d
- relative: mild-moderate neurologic diathesis or thrombocytopenia, brain metastases, recent major trauma, major abdominal surgery within page 2 d, GI/GU bleed within 14 d, endocarditis, severe HTN (sBP >200 or dBP >120), recent stroke

Treatment of Pulmonary Embolism

- see Respirology, R20

Common Medications that Interact with Warfarin

- Acetaminophen (interaction with vitamin K metabolism)
- Alemtuzumab
- NSAIDs (GI injury)
- Fluconazole
- Metronidazole
- Sulfamethoxazole
- Tamoxifen

Initiation of Warfarin Therapy Requires Overlap with Heparin Therapy for 4-5 d

- 10 mg loading dose of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state
- Warfarin decreases Factor VII levels in first 48 h INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after ~4 d)

Low Risk Surgical Patients

- <40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal, or thoracic surgery

Moderate Risk Surgical Patients

- >40 yr, >1 risk factor for VTE, GA >30 min

High Risk Surgical Patients

- > yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency, or other risk factor

High Risk Medical Patients

- Heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, BD)
Hypercoagulable Disorders

Hypercoagulability Workup – Venous Thrombosis

- workup for malignancy or hypercoagulable state indicated for idiopathic VTE in presence of the following: age <50, recurrent VTE, family history of VTE and age <50, unusual site of DVT (portal, hepatic, mesenteric vascular beds), heparin-resistant disease (AT deficiency), warfarin-induced skin necrosis or neonatal purpura fulminans (proteins C or S deficiency); consider for women with VTE within 12 mo of exposure to OCP
- workup
  - initial
    - CBC, blood smear, coagulation studies, liver/renal function, urinalysis, fasting homocysteine
    - malignancy workup (see sidebar)
    - antiphospholipid antibodies (APLA): anticardiolipin antibodies (ACA) and lupus anticoagulant (LA)
    - activated protein C resistance (APCR)
    - DNA/Molecular: FVL (Factor V Leiden), PT (prothrombin G20210A), JAK-2
    - Flow Cytometry: PNH
    - post initial insult (>72 h) (as protein levels depleted/consumed by clot)
      - antithrombin (not on heparin)
      - Factor VIII (increased levels predict recurrence)
      - post-treatment
        - proteins C, S (not on warfarin)
- Note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state. Thus more focus is on the reversible/treatable causes (APLA, cancer, etc.)

CAUSES OF HYPERCOAGULABILITY LEADING TO VENOUS THROMBOEMBOLISM

Activated Protein C Resistance (Factor V Leiden)
- most common cause of hereditary thrombophilia
- 5% of general population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

Prothrombin (PT) G20210A
- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Protein C and Protein S Deficiency
- protein C inactivates Factor Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous: neonatal purpura fulminans
  - heterozygous:
    - type I: decreased protein C levels
    - type II: decreased protein C activity
    - acquired: liver disease, sepsis, DIC, warfarin
    - 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, warfarin

Antithrombin Deficiency
- antithrombin slowly inactivates thrombin in the absence of heparin, rapidly inactivates thrombin in the presence of heparin
- autosomal dominant inheritance or urinary losses in nephrotic syndrome
  - type I: decreased AT levels
  - type II: decreased AT activity
  - diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
  - deficiency may result in resistance to unfractionated heparin (LMWH must be used)

Elevated Factor VIII Levels
- an independent marker of increased thrombotic risk
- genetic basis for increased levels poorly understood

Disorders of Fibrinolysis
- include congenital plasminogen deficiency, tissue plasminogen activator deficiency

Antiphospholipid Antibody Syndrome (APS)
- definition: ≥1 clinical and ≥1 laboratory criteria
  - clinical: thrombosis, spontaneous abortions, fetal loss, premature birth before 34 wk
  - laboratory: antiphospholipid or lupus anticoagulant antibodies
  - mechanism: not well understood, antibodies interact with platelet membrane phospholipid causing increased adhesion and aggregation; can also interfere with action of proteins C and S
- see Rheumatology, RH12

Common Causes of Hypercoagulability

- CALM APES
  - Protein C deficiency
  - Antiphospholipid Ab
  - Factor V Leiden
  - Malignancy
  - Antithrombin deficiency
  - Prothrombin G20210A
  - Increased Factor VIII (Eight)
  - Protein S deficiency

Although lupus anti-coagulant prolongs PTT, its main clinical feature is thrombosis

Protein C, protein S, and ATIII are decreased during acute thrombosis – therefore to test for deficiency, must be tested outside of this time period

Causes of Both Venous and Arterial Thrombosis include:

- Antiphospholipid antibodies
- Myeloproliferative neoplasms
- Heparin induced thrombocytopenia
- Distal venous clot with patent foramen ovale

Malignancy is a common cause of acquired hypercoagulability

Workup may include (controversial):
- Complete history and physical
- Routine blood work
- Urinalysis
- CXR and abdominal ultrasound
- Age appropriate screening: mammogram, Pap, PSA, colonoscopy
- Close follow-up

Disorders of Fibrinolysis
- include congenital plasminogen deficiency, tissue plasminogen activator deficiency

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**Hematologic Malignancies and Related Disorders**

**Acute Myeloid Leukemia**

**Definition**
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

**Epidemiology**
- incidence increases with age; median age of onset is 65 yr old
- accounts for 10-15% of childhood leukemias

**Risk Factors**
- myelodysplastic syndromes (MDS), benzene, radiation, alkylating agents as treatment for previous malignancy

**Pathophysiology**
- etiology subdivided into
  - primary: *de novo*
  - secondary: hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; tumor lysis syndrome

**Clinical Features**
- anemia, thrombocytopenia (associated with DIC in PML), neutropenia (even with normal WBC), leads to infections, fever
- thrombocytopenia (associated with DIC in promyelocytic leukemia)
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - hepatosplenomegaly (in AML)
  - lymphadenopathy (not marked)
- skin: leukemia cutis
- gonads (in ALL)
- eyes: Roth spots, cotton wool spots, vision changes (uncommon)
- leukostasis/hyperleukosis syndrome (medical emergency)
- large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, priapism

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**Typical Age of Presentation of Leukemias**
- ALL: Children and older adults
- CML: 40-60 yr
- AML, CLL: >60 yr

**Leukemia:** malignancies arise in bone marrow and may spread elsewhere (including blood and lymphoid tissue)

**Lymphoma:** malignancies arise in lymph nodes and lymphoid tissues and may spread elsewhere (including blood and bone marrow)

**BUT** the location where the malignant cells are found does not solely define the type of hematologic malignancy – classified based on the characteristics of the cell (histology, histochemistry, immunophenotyping, cytogenetics, molecular changes)

**Acute Leukemia**
**Definition (WHO):** presence of 20% blast cells or greater in bone marrow at presentation
**Classification:** divided into myeloid (AML) and lymphoid (ALL) depending on whether blasts are myeloblasts or lymphoblasts, respectively

**Auer rods are pathognomonic for AML**

**2008 WHO Classification of AML and Related Neoplasms**
- AML with recurrent genetic abnormalities
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
- AML, not otherwise specified (equivalent FAB classification)
  - Undifferentiated (M1)
  - Myeloblastic (M2)
  - Promyelocytic (M3)
  - Myelomonocytic (M4)
  - Monocytic (M5)
  - Erythroleukemic (M6)
  - Megakaryocytic (M7)
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
• metabolic effects; aggravated by treatment (rare)
  ▪ increased uric acid → nephropathy, gout
  ▪ release of phosphate → decreased Ca\textsuperscript{2+}, decreased Mg\textsuperscript{2+}
  ▪ release of procoagulants → DIC (higher risk in acute promyelocytic leukemia)
• decreased or normal K\textsuperscript{+} before treatment, increased K\textsuperscript{+} after treatment (from lysed cells)

**Investigations**
• blood work
  ▪ CBC: anemia, thrombocytopenia, variable WBC
  ▪ INR, aPTT, fibrin degradation products (FDP), fibrinogen (in case of DIC)
  ▪ increased LDH, increased uric acid, increased PO\textsubscript{4}\textsuperscript{3-} (released by leukemic blasts), decreased Ca\textsuperscript{2+}
  ▪ baseline renal and liver function tests
• peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
• bone marrow aspirate
  ▪ blast count: AML >20% (normal is <5%)
  ▪ morphologic, cytochemical, and/or immunotypic features are used to establish lineage and maturation (see sidebar for WHO classification of AML, H37)
• CXR to rule out pneumonia, ECG, MUGA scan prior to chemotherapy (cardiotoxic)

**Treatment**
• mainstay of treatment is chemotherapy (rapidly fatal without treatment)
  ▪ all AML subtypes treated similarly except promyelocytic variant with t(15:17) translocation
    ▪ all-trans-retinoic acid (ATRA) added to induce differentiation; arsenic trioxide + ATRA combination therapy for APL is non-inferior to traditional chemotherapy
• treatment strategy
  1. **Induction:** chemotherapy to induce complete remission of AML (see sidebar)
     ▪ several possible regimens (e.g. cytarabine with anthracycline [daunorubicin])
     ▪ patients with poor response to initial induction therapy – worse prognosis
     ▪ must ensure reversal of DIC, platelet transfusions if <10
  2. **Consolidation:** to prevent recurrence
     ▪ intensive consolidation chemotherapy
     ▪ stem cell transplantation – autologous or allogeneic (younger patients with better performance status)
     ▪ consider acceleration with hematopoietic growth factors (e.g. G-CSF) if severe infection develops
• supportive care
  ▪ screening for infection via regular C&S of urine, stool, sputum, oropharynx, catheter sites, perianal area
  ▪ fever: C&S of all orifices, CXR, start antibiotics
  ▪ platelet and RBC transfusions (irradiated to prevent transfusion-related GVHD) ± EPO
  ▪ prevention and treatment of metabolic abnormalities
    ▪ allopurinol, rasburicase for prevention of hyperuricemia

**Prognosis**
• achievement of first remission
  ▪ 70-80% if ≤60 yr old, 50% if >60 yr old
  ▪ median survival 12-24 mo
  ▪ 5 yr survival 40%
• prognosis related to cytogenetics (favorable, intermediate, or adverse)

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**Myelodysplastic Syndromes**

**Definition**
• heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias
• syndromes defined according to World Health Organization (WHO) classifications (see sidebar)

**Pathophysiology**
• disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular)
• intramedullary apoptosis: programmed cell death within bone marrow
  ▪ both processes lead to reduced mature cells in periphery
  ▪ <30% develop AML

**Risk Factors**
• elderly, post-chemotherapy, benzene or radiation exposure
• occurs in 60/100,000 in patients >60 yr old
Clinical Features
- insidious onset: associated with those of pancytopenia
- infections and bleeding out of proportion with peripheral blood counts

Investigations
- diagnosed by
  - anemia ± thrombocytopenia ± neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bilobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size and cytoplasm (e.g. giant hypogranular platelets)
- bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
  - bone marrow: dysplastic and often normocellular/hypercellular
  - cytogenetics: partial or total loss of chromosomes 5, 7, Y, or trisomy 8

Prognosis
- Revised International Prognostic Scoring System (IPSS-R) uses 5 factors to estimate mean survival
  - cytology, % bone marrow blasts, hemoglobin, platelets, absolute neutrophil count
  - based on the calculated score, a patient’s MDS prognostic risk is “Very Low”, “Low”, “Intermediate”, “High”, or “Very High” with a mean survival of 8.7, 5.3, 3.0, 1.6, and 0.8 yr, respectively

Treatment
- low risk of transformation to acute leukemia (IPSS-R Very Low or Low)
  - erythropoietin stimulating agents weekly is first line in reducing transfusion requirements
  - 5q(-) cytogenetic: lenalidomide PO
  - supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- high risk of transformation to acute leukemia (IPSS-R Intermediate, High or Very High)
  - supportive care
  - stem cell transplantation if age <65 yr
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacytidine), histone deacetylase inhibitors

Myeloproliferative Neoplasms

Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets, and other cells of myeloid lineage)

Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)

Prognosis
- may develop marrow fibrosis with time
- all disorders may progress to AML

Table 31. Chronic Myeloproliferative Disorders

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<tr>
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<th>CML</th>
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<tr>
<td>Genetic Association</td>
<td>bcr-abl mut. (90%+)</td>
<td>JAK2 mut. (95%)</td>
<td>JAK2 mut. (~50%)</td>
<td>JAK2 mut. (~50%)</td>
</tr>
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</table>

CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; PV = polycythemia vera
Chronic Myeloid Leukemia

Definition
• myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

Epidemiology
• occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

Pathophysiology
• Philadelphia chromosome (Ph)
  • translocation between chromosomes 9 and 22
  • the c-abl proto-oncogene is translocated from chromosome 9 to “breakpoint cluster region” (bcr) of chromosome 22 to produce bcr-abl fusion gene, an active tyrosine kinase

Clinical Features
• 3 clinical phases
  • **chronic phase**: 85% diagnosed here
    • few blasts (<10%) in peripheral film
    • ± slightly elevated eosinophils and basophils
  • **accelerated phase**: impaired neutrophil differentiation
    • circulating blasts (10-19%) with increasing peripheral basophils (pruritus)
  • **blast crisis**: more aggressive course, blasts fail to differentiate
    • blasts (>20%) in peripheral blood or bone marrow; reflective of acute leukemia (1/3 ALL, 2/3 AML)
  • **clinical presentation**
    • 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
    • nonspecific symptoms
      • fatigue, weight loss, malaise, excessive sweating, fever
    • secondary to splenic involvement
      • early satiety, LUQ pain/fullness, shoulder tip pain (referred)
      • splenomegaly (most common physical finding)
    • anemia
    • bleeding: secondary to platelet dysfunction
    • pruritus, PUD: secondary to increased blood histamine
    • leukostasis, priapism, encephalopathy (rare): secondary to very elevated WBC (rare)

Investigations
• high increase in WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
• WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
• peripheral blood film
  • leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
• presence of different mid-stage progenitor cells differentiates it from AML
• bone marrow
  • myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
  • molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
• abdominal imaging for spleen size

Treatment
• symptomatic
  • allopurinol and antihistamines
• chronic phase
  • imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for bcr-abl
    • if loss of response or intolerance (~25%), trial of 2nd (dasatinib, nilotinib) or 3rd generation inhibitors
    • dasatinib may be considered for first line management (see sidebar)
  • interferon-α: may improve response to tyrosine kinase inhibitors
  • hydroxyurea in palliative setting
  • bone marrow transplantation if progression to accelerated or blast phases: CML (curative)
• accelerated phase or blast phase
  • refer for clinical trial or 2nd/3rd generation (ponatinib only for T315I-mutated CML) TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard AML induction
  • stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones

Detection of the bcr-abl fusion gene is a diagnostic test for CML (present in over 90% of patients)

Early Response with Dasatinib or Imatinib in Chronic Myeloid Leukemia
Blood 2014;123:494-500
Study: The DASatinib vs. Imatinib Study in Treatment-Naïve CML patients (DASISION) trial is a randomized phase 3 trial comparing treatment with dasatinib (n=259) or imatinib (n=260) once daily in patients with newly diagnosed CML in chronic phase.
Results: Dasatinib was associated with superior efficacy during the first year of treatment, including significantly higher complete cytogenetic responses (63% vs. 72%) and major molecular responses (64% vs. 28%) compared to imatinib, respectively. Dasatinib was associated with faster and deeper responses at 3, 6, and 12 mo.
Clinical Features
• symptoms are secondary to high red cell mass and hyperviscosity (see Erythrocytosis, H6)
  • bleeding complications: epistaxis, gingival bleeding, echymoses, and GI bleeding
  • due to platelet abnormalities
  • thrombotic complications: DVT, PE, thrombophlebitis, increased incidence of stroke, MI
  • due to increased blood viscosity, increased platelet number and/or activity
  • erythromelalgia (burning pain in hands and feet and erythema of the skin)
  • associated with platelets >400,000/mm³
  • pathognomonic microvascular thrombotic complication in PV and ET
• pruritus, especially after warm bath or shower (40%)
• due to cutaneous mast cell degranulation and histamine release
• epigastric distress, PUD
• due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow
• due to increased blood viscosity
• gout (hyperuricemia)
• due to increased cell turnover
• characteristic physical findings
  • plethora (ruddy complexion) of face (70%), palms
  • splenomegaly (70%), hepatomegaly (40%)

Investigations
• see Erythrocytosis, H6
• must rule out secondary polycythemia
• diagnosis (WHO 2008) requires either both major criteria plus one minor criteria OR the first major criterion plus 2 minor criteria
  • Major Criteria
    1. hemoglobin >18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume
    2. presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation
  • Minor Criteria
    1. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
    2. serum erythropoietin level below the reference range for normal
    3. endogenous erythroid colony formation in vitro

Treatment
• phlebotomy to keep hematocrit <45%
• hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
• low-dose Aspirin® (for antithrombotic prophylaxis, will also treat erythromelalgia)
• allopurinol: as needed
• antihistamines: as needed

Prognosis
• 10-20 yr survival with treatment
• complicated by thrombosis, hemorrhage, leukemia transformation (AML)
**Idiopathic Myelofibrosis**

**Definition**
- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

**Epidemiology**
- rare, median age at presentation is 65 yr

**Pathophysiology**
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (primitive RBCs and WBCs present in blood)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)
  - mutations in JAK2, c-mpl, and calreticulin define the clone

**Clinical Features**
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal HTN
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

**Investigations**
- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B12 (2° to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets, and megakaryocyte fragments
- JAK2 PCR
- bone marrow aspirate: “dry tap” in as many as 50% of patients (no blood cells aspirated)
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

**Treatment**
- allogeneic stem cell transplant is potentially curative
- JAK2 inhibitors
- symptomatic treatment
  - transfusion for anemia
  - erythropoietin: 30-50% of patients respond
  - androgens (e.g., danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, systemic symptoms
  - α-interferon (as second line therapy)
  - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis, symptomatic splenomegaly
  - thalidomide, and etanercept may improve quality of life and spleen size, but not survival

**Prognosis**
- International Prognostic Scoring System (IPSS) for IMF uses 5 factors to determine mean survival
  - presence of constitutional symptoms; age >65; hemoglobin <10.0 g/dL; leukocyte count >25,000/mm3; circulating blast cells ≥1%
  - based on the calculated score, a patient's IMF is categorized as “low,” “intermediate 1,” “intermediate 2,” or “high” with a mean survival of 135, 95, 48, and 27 mo respectively
  - risk of transformation to AML (8-10%)

**Essential Thrombocytemia**

**Definition**
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocytemia
Clinical Features

- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky color, usually worse with heat, caused by platelet activation → microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI, associated with platelets >1,000,000/mm^3)
- constitutional symptoms, splenomegaly
- pregnancy complications; increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

Treatment

- low dose ASA if previous history of thrombotic event, ≥1 cardiovascular risk factors, older, or symptomatic
- cytoreductive therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st line therapy), anagrelide, interferon-α, or 32P (age >80 or lifespan <10 yr)
- splenectomy not recommended (increased risk of bleeding episodes, thrombosis)

Lymphoid Malignancies

Acute Lymphoblastic Leukemia

Definition

- malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
  1. B-cell: precursor B lymphoblastic leukemia
  2. T-cell: precursor T lymphoblastic leukemia
- The French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged, as WHO subdivides ALL into two types depending on cell of origin

Clinical Features

- see Acute Myeloid Leukemia, H37 for full list of symptoms
- distinguish ALL from AML based on Table 32
- clinical symptoms usually secondary to:
  - bone marrow failure: anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), thrombocytopenia
  - organ infiltration: tender bones, lymphadenopathy, hepatosplenomegaly, meningeval signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations

- CBC: increased leukocytes >10 x 10^9/L (occurs in 50% of patients); neutropenia, anemia, or thrombocytopenia
- may have increased uric acid, K^+, PO_4^3-, Ca^{2+}, LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- cytogenetics: Philadelphia (Ph) chromosome in ~25% of adult ALL cases
• CXR: patients with ALL may have a mediastinal mass
• LP prior to systemic chemotherapy to assess for CNS involvement (ensure adequate platelet count and PT/PTT)

Treatment
• eliminate abnormal cloned cells
  1. Induction: to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
  2. Consolidation and/or intensification chemotherapy
     • consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
     • intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. Maintenance chemotherapy: low dose intermittent chemotherapy over prolonged period (2-3 yr) to prevent relapse
  4. Prophylaxis: Methotrexate (intrathecal or systemic) or CNS radiation therapy
     • hematopoietic stem cell transplantation: potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

Prognosis
• depends on response to initial induction or if remission is achieved following relapse
• good prognostic factors: young, WBC  $< 30 \times 10^9/L$, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
• achievement of first remission: 60-90%
• childhood ALL: 80% long-term remission (>5 yr)
  • higher cure rates in children because of better chemotherapy tolerance, lower prevalence of \( bcr-abl \) fusion gene (associated with chemotherapeutic resistance)
• adult ALL: 30-40% 5 yr survival

Table 32. Differentiating AML From ALL

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big people (adults)</td>
<td>Small people (kids) but the incidence increases with age over 20</td>
</tr>
<tr>
<td>Big blasts</td>
<td>Small blasts</td>
</tr>
<tr>
<td>Big mortality rate</td>
<td>Small mortality rate (kids)</td>
</tr>
<tr>
<td>Lots of cytoplasm</td>
<td>Less cytoplasm</td>
</tr>
<tr>
<td>Lots of nuclei (3-5)</td>
<td>Few nuclei (1-3)</td>
</tr>
<tr>
<td>Lots of granules and Auer rods</td>
<td>No granules</td>
</tr>
<tr>
<td>Maturation defect beyond myeloblast or promyelocyte</td>
<td>Maturation defect beyond lymphoblast</td>
</tr>
</tbody>
</table>

Lymphomas

Definition
• collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
  • leading to lymphadenopathy, extranodal disease, and constitutional symptoms

Table 33. Ann Arbor System for Staging Lymphomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or extralymphatic organ or site</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm; may or may not be accompanied by single extra lymphatic site or splenic involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse involvement of one or more extralymphatic organs including bone marrow</td>
</tr>
</tbody>
</table>

• subtypes
  • A = absence of B-symptoms (see Approach to Lymphadenopathy, H12)
  • B = presence of B-symptoms

Hodgkin is distinguished from non-Hodgkin lymphoma by the presence of Reed-Sternberg cells
Table 34. Chromosome Translocations

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Gene Activation</th>
<th>Associated Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>c-myc activation</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>bcl-2 activation</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>Philadelphia chromosome (bcr-abl hybrid)</td>
<td>CML, ALL in adults (25% of the time)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Overexpression of cyclin D1 protein</td>
<td>Mantle cell lymphoma</td>
</tr>
</tbody>
</table>

Hodgkin Lymphoma

Definition
- malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal center B-cells)

Epidemiology
- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases, causal role not determined

Clinical Features
- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
  - splenomegaly (50%) ± hepatomegaly
- mediastinal mass
  - found on routine CXR, may be symptomatic (cough)
  - rarely may present with SVC syndrome, pleural effusion
- systemic symptoms
  - B symptoms (especially in widespread disease; fever in 30%), pruritus
  - non-specific/paraneoplastic
  - alcohol-induced pain in nodes, nephrotic syndrome
  - starts at a single site in lymphatic system (node), spreads first to adjacent nodes
  - disease progresses in contiguity with lymphatic system

Investigations
- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, leukocytosis, platelets normal or increased early, decreased in advanced disease
- biochemistry
  - HIV serology
  - LFTs (liver involvement)
  - RFTs (prior to initiating chemotherapy)
  - ALP, Ca²⁺ (bone involvement)
  - ESR, LDH (monitor disease progression)
- imaging
  - CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), gallium scan (assess treatment response), PET scans
  - cardiac function assessment (MUGA scan or echocardiography): for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, ČVA), treatment can be cardiotoxic
  - PFTs: if history of lung disease (COPD, smoking, previous radiation to lung)
  - excisional lymph node biopsy confirms diagnosis
  - bone marrow biopsy to assess marrow infiltration (only necessary if B-symptoms, stage III or IV, bulky disease or cytopenia)

Treatment
- stage I-II: chemotherapy (ABVD) followed by involved field radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD) with XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy, bone marrow transplant
- new imaging modalities increasingly used including PET scans used to follow response to treatment

Complications of Treatment
- cardiac disease: secondary to XRT, adriamycin is also cardiotoxic
- pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
- infertility: recommend sperm banking
- secondary malignancy in irradiated field
  - <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  - solid tumors of lung, breast; >8 yr after treatment
- non-Hodgkin lymphoma
- hypothyroidism: post XRT
**Prognosis**

- **Hasenclever adverse prognostic factors**
  1. serum albumin <40 g/L (4 g/dL)
  2. hemoglobin <105 g/L (10.5 g/dL)
  3. male
  4. stage IV disease
  5. age ≥45 yr
  6. leukocytosis (WBC >1,500/mm³)
  7. lymphocytopenia (lymphocytes <60/mm³ or <8% of WBC count or both)

- **prognostic score**
  - each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)

**Non-Hodgkin Lymphoma**

**Definition**

- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

**Classification**

- multiple classification systems exist at present and may be used at different centers
- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt’s lymphoma, mantle cell lymphoma
  - T-cell NHL: e.g. mycosis fungoides, anaplastic large cell lymphoma
- WHO/REAL classification system: 3 categories of NHLs based on natural history
  - **indolent** (35-40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL
  - **aggressive** (~50% of NHL): e.g. diffuse large B-cell lymphoma
  - **highly aggressive** (~5% of NHL): e.g. Burkitt’s lymphoma
- Note: mantle cell lymphoma (7% of NHL) may have features of aggressive or indolent lymphoma

**Clinical Features**

- painless superficial lymphadenopathy, usually >1 lymph node region
- usually presents as widespread disease (exception is aggressive lymphoma)
- constitutional symptoms not as common as in Hodgkin lymphoma
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when bone marrow is involved
- abdominal signs
  - hepatosplenomegaly
  - retroperitoneal and mesenteric involvement (second most common site of involvement)
  - oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
  - extranodal involvement: most commonly GI tract; also testes, bone, kidney
  - CNS involvement in 1% (often with HIV)

**Investigations**

- **CBC**
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic anemia
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood is valuable for low-grade NHL
- biochemistry
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease, poor prognostic factor)
- CXR, CT neck, abdomen, pelvis for staging
- PET is useful for monitoring response to treatment and evaluation of residual tumor following therapy in aggressive histological disease
- diagnosed by
  - lymph node biopsy: excisional biopsy preferred, FNA unreliable
  - bone marrow biopsy: not optimal for diagnosis as BM may not be involved

**Treatment**

- localized disease (e.g. GI, brain, bone, head and neck)
  - radiotherapy to primary site and adjacent nodal areas
  - adjuvant chemotherapy
  - surgery: splenic marginal zone lymphoma

---

**International Prognostic Factors Project 1998**

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
</tr>
<tr>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>51%</td>
</tr>
<tr>
<td>5-7</td>
<td>42%</td>
</tr>
</tbody>
</table>

FFP = freedom from progression at 5 yr

---

**NHL: Associated Conditions**

- Immunodeficiency (e.g. HIV)
- Autoimmune diseases (e.g. SLE)
- Infections (e.g. EBV)

---

**CHOP-Like Chemotherapy With or Without Rituximab in Young Patients with Good-Prognosis Diffuse Large B-Cell Lymphoma (MINIT)**

**Lancet Oncol** 2011;12:1013-1022

**Study**: International RCT with a median follow-up of 72 mo.

**Participants**: 824 patients with good-prognosis diffuse large B-cell lymphoma who had ≤1 risk factor, stage II-IV disease, or stage I disease with bulk (age 18-60 yr).

**Intervention**: Patients received either 6 cycles of CHOP-like chemotherapy and rituximab (CCR; n=413) or 6 cycles of CHOP-like chemotherapy alone (CLC; n=411). Bulky and extranodal sites received additional radiotherapy.

**Primary Outcome**: Event-free survival.

**Results**: Patients receiving CCR had an increased 6 yr event-free survival compared with the CLC group (74.3% vs. 55.8%; p<0.0001). Event-free survival was affected by treatment group, presence of bulky disease, and age-adjusted International Prognostic Index (IPI). Overall survival was affected by treatment group and presence of bulky disease. Within the CCR group, a favorable subgroup (IPI=0, no bulk) and less favorable subgroup (IPI=1 or bulk, or both) could be defined; event-free survival was 84.3% vs. 71.0%.

**Conclusion**: Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large B-cell lymphoma. The definition of two prognostic subgroups allows a more refined therapeutic approach to these patients than does assessment by IPI alone.
- **indolent lymphoma**: goal of treatment is symptom management
  - watchful waiting
  - radiation therapy for localized disease
  - bendamustine plus rituximab, an anti-CD20 antibody, is superior to CHOP + rituximab (CHOP-R) for advanced stage disease (StIL trial)

- **aggressive lymphoma**: goal of treatment is curative
  - combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma; different regimens for mantle cell lymphoma
  - radiation for localized/bulky disease
  - CNS prophylaxis with high-dose methotrexate if certain sites involved (testicular, nasopharyngeal)
  - relapse, resistant to therapy: high dose chemotherapy, BMT

- **highly aggressive lymphoma**
  - Burkitt lymphoma: short bursts of intensive chemotherapy
  - "CODOX-M" chemotherapy regimen also often used ± IVAC
  - CNS prophylaxis and tumor lysis syndrome prophylaxis

**Complications**
- hypersplenism
- infection
- autoimmune hemolytic anemia and thrombocytopenia
- vascular obstruction (from enlarged nodes)
- tumor lysis syndrome (particularly in very aggressive lymphoma) – see H52

**Prognosis**
- follicular lymphoma: Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60; number of nodal areas >4; elevated LDH; Ann Arbor stage III-IV; hemoglobin <120 g/L
  - based on calculated risk, mean 5 yr survival ranges from 53-91%
  - rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphoma such as diffuse large B-cell lymphoma
- diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
  - based on calculated risk, mean 5 yr survival ranges from 26-73%
  - has ~40% rate of cure

**Table 35. Characteristics of Select Non-Hodgkin Lymphomas**

<table>
<thead>
<tr>
<th>Percentage of NHLs</th>
<th>Follicular Lymphoma</th>
<th>Diffuse Large B-Cell Lymphoma (DLBCL)</th>
<th>Burkitt Lymphoma</th>
<th>Mantle Cell Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22-30%</td>
<td>33%</td>
<td>&lt;1% adult NHLs 30% childhood NHLs</td>
<td>6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genetic Mutation</th>
<th>Bcl-2 activation</th>
<th>Bcl-2, Bcl-6, MYC rearrangements</th>
<th>c-myc activation</th>
<th>Overexpression of cyclin D1 (Bcl-1 activation)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>Indolent</th>
<th>Aggressive (high-grade)</th>
<th>Very aggressive</th>
<th>Indolent</th>
</tr>
</thead>
</table>

|------------------|----------------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------|

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Widespread painless LAD + bone marrow involvement</th>
<th>Rapidly progressive LAD and extranodal infiltration 50% present at stage IV 100% widely disseminated</th>
<th>Endemic form: massive jaw LAD &quot;Starry-sky&quot; histology High-risk of tumor lysis syndrome upon treatment</th>
<th>Often presents Stage IV with palpable LAD Involvement of GI tract (lymphomatosis polyposis), Waldeyer’s Ring Extremely aggressive, 5 yr survival 25%</th>
</tr>
</thead>
</table>

*LAD = lymphadenopathy*
Table 36. Characteristics of B-Cell Malignant Proliferation

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>CLL</th>
<th>Macroglobulinemia</th>
<th>Myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>IgM if present</td>
<td>IgM</td>
<td>IgG, A, light chain (rarely M, D, or E)</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>Very common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Hepatosplenomegaly</td>
<td>Common</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Bone Lesions</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Immunoglobulin Complications</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Chronic Lymphocytic Leukemia

Definition
- indolent disease characterized by clonal malignancy of mature B-cells

Epidemiology
- most common leukemia in Western world
- mainly older patients; median age 65 yr
- M>F

Pathophysiology
- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes, and spleen

Clinical Features
- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C or night sweats for ≥2 wk without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (Coombs positive), ITP, hypogammaglobulinemia ± neutropenia
- bone marrow failure: late, secondary to marrow involvement by CLL cells

Investigations
- CBC: clonal population of CLL lymphocytes >5 x 10^9/L
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry (CD5, CD20, CD23, etc.)
- cytogenetics: FISH (dictates response therapy and prognosis)
- bone marrow aspirate
  - lymphocytes >30% of all nucleated cells
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis), or mixed (25%)

Natural History and Treatment
- natural history: indolent but incurable, with slow progression; thus select gentlest treatment that will control symptoms
  - observation if early, stable, asymptomatic
  - intermittent chlorambucil or fludarabine chemotherapy combined with rituximab, chlorambucil in the elderly
  - corticosteroids, IVIg: especially for autoimmune phenomena
  - radiotherapy
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- 9 yr median survival, but varies greatly
• prognosis predicted by Rai staging
  ▪ low risk: lymphocytosis in blood and bone marrow only
  ▪ intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
  ▪ high risk: lymphocytosis with disease-related non-immune-mediated anemia (<11.0 g/dL) or thrombocytopenia (<100,000/mm^3)
• molecular therapies
  ▪ Idelalisib – PI3K inhibitor (not FDA-approved)
  ▪ Ibrutinib – BTK (Bruton's tyrosine kinase) inhibitor (FDA-approved in relapsed setting)

Complications
• bone marrow failure
• immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia, impaired T-cell function)
• polyclonal or monoclonal gammopathy (often IgM)
• hyperuricemia with treatment
• 5% undergo Richter’s transformation: aggressive transformation to diffuse large B-cell lymphoma (see Table 35)

### Multiple Myeloma

#### Definition
• neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
• usually single clone of plasma cells, although biclonal myeloma also occurs; rarely non-secretory

#### Epidemiology
• incidence 3 per 100,000, most common plasma cell malignancy
• increased frequency with age; median age of diagnosis is 68 yr; M>F

#### Pathophysiology
• malignant plasma cells secrete monoclonal antibody
  ▪ 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
  ▪ IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
  ▪ 15-20% produce free light chains or light chains alone found in either:
    - serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
    - urine has Bence-Jones protein
  ▪ <5% are non-secretory

#### Clinical Features and Complications
• bone disease: pain (usually back), bony tenderness, pathologic fractures
  ▪ lytic lesions are classical (skull, spine, proximal long bones, ribs)
  ▪ increased bone resorption secondary to osteoclast activating factors such as PTHrP
• anemia: weakness, fatigue, pallor
  ▪ secondary to bone marrow suppression
• weight loss
• infections
  ▪ usually S. pneumoniae and Gram-negatives
  ▪ secondary to suppression of normal plasma cell function
• hypercalcemia: N/V, confusion, constipation, polyuria, polydipsia
  ▪ secondary to increased bone turnover
• renal disease/renal failure
  ▪ most frequently causes cast nephropathy (see Nephrology, NP30)
• bleeding
  ▪ secondary to thrombocytopenia, may see petechiae, purpura
  ▪ can also be caused by acquired von Willebrand disease
• extramedullary plasmacytoma
  ▪ soft tissue mass composed of monoclonal plasma cells, purplish color
• hyperviscosity: may manifest as headaches, stroke, angina, MI
  ▪ secondary to increased viscosity caused by M protein
• amyloidosis
  ▪ accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  ▪ may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)

#### CRAB
- Increased Calcium
- Renal failure
- Anemia
- Bone lesions (lytic lesions or osteoporosis felt to be caused by myeloma)

Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis.

### Amyloid
The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues. Found in a variety of clinical disorders and can cause systemic (e.g., MM [light chains]) or localized amyloidosis (e.g., Alzheimer disease [AB amyloid]).
• neurologic disease: muscle weakness, pain, paresthesias
  ▪ radiculopathy caused by vertebral fracture, extramedullary plasmacytoma
  ▪ spinal cord compression (10-20% of patients) is a medical emergency

**Investigations**

- CBC
  ▪ normocytic anemia, thrombocytopenia, leukopenia
  ▪ rouleaux formation on peripheral film
- biochemistry
  ▪ increased Ca\(^{2+}\), increased ESR, decreased anion gap, increased Cr, albumin, \(\beta_2\)-microglobulin
  (as part of staging), proteinuria (24 h urine collection)
- monoclonal proteins
  ▪ serum protein electrophoresis (SPEP): demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  ▪ urine protein electrophoresis (UPEP): demonstrates light chains in urine = Bence-Jones protein (15% secrete only light chains)
  ▪ immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  ▪ serum free light chain quantification: kappa and lambda light chains, calculated ratio
- bone marrow aspirate and biopsy
  ▪ often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for FISH or cytogenetics (prognostic implications)
- skeletal series (x-rays), MRI if symptoms of cord compression
  ▪ presence of lytic lesions and areas at risk of pathologic fracture
  ▪ bone scans are not useful since they detect osteoblast activity
- \(\beta_2\)-microglobulin, LDH, and CRP are poor prognosticators

**Diagnosis**

- International Myeloma Working Group Criteria
  1. serum or urinary monoclonal protein
  2. presence of clonal plasma cells in bone marrow or a plasmacytoma
  3. presence of end-organ damage related to plasma cell dyscrasia, such as
    ▪ increased serum Ca\(^{2+}\)
    ▪ lytic bone lesions or osteoporosis
    ▪ anemia
    ▪ renal failure

**Treatment**

- treatment is non-curative
- treatment goals
  ▪ improvement in quality of life (improve anemia, reverse renal failure, bony pain)
  ▪ prevention of progression and complications
  ▪ increase overall survival
- autologous stem cell transplant as consolidation therapy
  ▪ usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents
    ▪ (i.e. immunomodulatory drugs or proteosome inhibitors)
  ▪ chemotherapy if >65 yr old or transplant-ineligible
    ▪ melphalan, prednisone, and novel agent (i.e. bortezomib)
  ▪ dexamethasone and bortezomib if ARF; bortezomib ± dexamethasone in light chain amyloidosis
- supportive management
  ▪ bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  ▪ local XRT for bone pain, spinal cord compression
  ▪ kyphoplasty for vertebral fractures to improve pain relief and regain height
  ▪ treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia, DVT prophylaxis
  ▪ all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient’s comorbidities, and preferences

**Prognosis**

- International Staging System (\(\beta_2\)-microglobulin and albumin) used to stage and estimate prognosis
  ▪ cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy)
  ▪ median survival based on stage, usually 16-70 mo
Monoclonal Gammopathy of Unknown Significance

**Definition**
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr of age
  - asymptomatic

**Diagnosis**
- presence of a serum monoclonal protein (M protein) at a concentration <3.0 g/dL
- <10% plasma cells in bone marrow
- absence of hyperCalcemia, Renal insufficiency, Anemia, Bone disease related to the plasma cell proliferative process (absence of “CRAB”)
- 0.3-1% of patients develop a hematologic malignancy each year
  - patients with M protein peak ≥1.5 g/dL or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with abnormal serum free light chains ratio are at increased risk of malignant transformation
- monitor with annual history, physical, CBC, Cr, calcium, albumin, serum protein electrophoresis (considered pre-malignant)

Lymphoplasmacytic Lymphoma (Waldenstrom’s Macroglobulinemia)

**Definition**
- proliferation of lymphoplasmacytoid cells
- presence of monoclonal IgM paraprotein

**Clinical Features**
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
- key complication to avoid: hyperviscosity syndrome
  - because IgM (unlike IgG) confined largely to intravascular space

**Investigations and Diagnosis**
- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- blood work rarely see hypercalcemia
- cold hemagglutinin disease possible: Raynaud's phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present

**Management**
- R-CVP, alkylating agents (chlorambucil), nucleoside analogues (fludarabine), thalidomide, rituximab, or combination therapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

**Definition**
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom's macroglobulinemia accounts for 85% of cases
Clinical Features
- hypervolemia causing: CHF, headache, lethargy, dilutional anemia
- CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, stroke
- retina shows venous engorgement and hemorrhages
- bleeding diathesis
  - due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
- ESR usually very low

Treatment
- plasmapheresis, chemotherapy

Tumor Lysis Syndrome

Definition
- group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
- more common in diseases with large tumor burden and high proliferative rate (high grade lymphoma, leukemia)

Clinical Features
- metabolic abnormalities
  - cells lyse, releasing K⁺, uric acid, PO₄³⁻ (increased levels)
  - PO₄³⁻ binds Ca²⁺ (decreased Ca²⁺)
- complications
  - lethal cardiac arrhythmia (increased K⁺)
  - acute renal failure (urate nephropathy, see Nephrology, NP30)

Treatment
- prevention
  - aggressive IV hydration
  - alkalization of the urine
  - allopurinol or rasburicase
  - correction of pre-existing metabolic abnormalities
- dialysis

Blood Products and Transfusions

Blood Products
- RBCs, platelets and coagulation factors (frozen plasma [FP], cryoprecipitate, factor concentrates) are available for transfusion
- donated blood (1 U = 450-500 mL) is fractionated into these various components
  - centrifugation separates whole blood into RBCs and platelet-rich plasma
  - platelet-rich plasma is further fractionated into platelets and plasma
    - need to pool together multiple units to obtain therapeutic amounts
    - FP (previously known as FFP) is plasma frozen within 24 h of collection
    - cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures

Specialized Products
- irradiated blood products
  - prevent proliferation of donor T-cells in potential or actual BMT recipients
  - used for immunocompromised patients or for patients on purine analogue chemotherapy, first-degree relatives, HLA-matched products and intrauterine transfusions, Hodgkin lymphoma
- CMV-negative blood products
  - potential transplant recipients
  - neonates
  - AIDS patients
  - seronegative pregnant women

<table>
<thead>
<tr>
<th>Blood Groups</th>
<th>Antigen (on RBC)</th>
<th>Antibody (in serum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>Anti-A, anti-B</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>Anti-B</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti-A</td>
</tr>
<tr>
<td>AB</td>
<td>A and B</td>
<td>Nil</td>
</tr>
</tbody>
</table>
**Red Blood Cells**

**Packed Red Blood Cells**
- stored at 4°C
- transfuse within 42 d of collection, otherwise cell lysis may result in hyperkalemia
- infuse each unit over 2 h, max of 4 h

**Indications for packed RBC Transfusion**
- Hb <7.0 g/dL; this may change as per patient’s tolerance or symptoms
  - maintain Hb between 7.0 and 10.0 g/dL during active bleeds
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding
  - impaired pulmonary function
  - increased O₂ consumption

**Selection of Red Cells for Transfusion**
- when a need for RBC transfusion is anticipated, the following should be ordered
  - group and screen: determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens in the patient’s serum
  - crossmatch: involves mixing the recipient’s blood with potential donor blood and looking for agglutination (takes 30–45 min)
- when blood is required, several options are available
  - 1st line: fully crossmatched blood, electronic crossmatch is becoming more widely used (not always available in emergency situations)
  - 2nd line: donor blood of the same group and Rh status as the recipient
  - 3rd line: O- blood for females of reproductive age; O+ blood for all others

**Platelets**

**Table 37. Platelet Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random donor (pooled)</td>
<td>Thrombocytopenia with bleeding</td>
</tr>
<tr>
<td>Single donor platelets</td>
<td>Potential BMT recipients</td>
</tr>
<tr>
<td>HLA matched platelets</td>
<td>Refractory to pooled or single donor platelets, presence of HLA antibodies</td>
</tr>
</tbody>
</table>

- stored at 20-24°C
- random donor platelets are transfused from a pool of 4 units; this should increase the platelet count by ≥15,000/mm³
- single donor platelets (transfused as single units) should increase the platelet count by 40-60,000/mm³
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies, consumption (bleeding, sepsis), or hypersplenism may be present

**Table 38. Indications for Platelet Transfusion**

<table>
<thead>
<tr>
<th>Plt (×10⁹)</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10,000</td>
<td>Non-immune thrombocytopenia</td>
</tr>
<tr>
<td>&lt;20,000</td>
<td>Procedures not associated with significant blood loss</td>
</tr>
<tr>
<td>&lt;50,000</td>
<td>Procedures associated with blood loss or major surgery (&gt;500 mL EBL)</td>
</tr>
<tr>
<td>&lt;100,000</td>
<td>Pre-neurosurgery or head trauma</td>
</tr>
<tr>
<td>Any</td>
<td>Platelet dysfunction (or antiplatelet agents) and marked bleeding</td>
</tr>
</tbody>
</table>

**Relative Contraindications of Platelet Transfusion**
- TTP, HIT, post-transfusion purpura, HELLP

---

1 unit of pRBC will increase Hb by approximately 10 g/L or increase Hct by 4%.

American Society of Hematology
Choosing Wisely Recommendation
Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin range (70-80 g/L) in stable noncardiac patients.

Transfusion Requirements in Critical Care (TRICC)
NEJM 1999;340:409-417
Study: Multicenter, RCT.
Participants: 839 critically ill patients with euolemia after initial treatment and hemoglobin less than 9 g/dL within 72 h of ICU admission.
Intervention: Patients receiving a transfusion followed either (1) a restrictive strategy (RS, n=418) in which red cells were transfused if hemoglobin was less than 7.0 g/dL and then maintained at 7.9 g/dL or (2) a liberal strategy (LS, n=420) in which transfusions occurred when the hemoglobin was less than 10.0 g/dL and then maintained at 10-12 g/L.
Primary Outcome: Mortality at 30 d and severity of organ dysfunction.
Results: Mortality rates at 30 d were similar between groups. However, mortality rates were significantly lower with the RS among less acutely ill patients (6.7% RS and 16.1% LS group; p=0.03) and among those less than 53 yr of age (5.7% RS and 13% LS; p=0.02), but did not differ in a subgroup with clinically significant cardiac disease.
Conclusion: A RS of red cell transfusion is at least as effective as, and possibly superior to, a LS transfusion in critically ill patients.

Liberal or Restrictive Transfusion in High-Risk Patients After Hip Surgery (FOCUS)
NEJM 2011;365:2453-2462
Study: Multicenter RCT.
Participants: 2,016 patients aged >50 yr with a history of or risk factors for cardiovascular disease and hemoglobin (Hb) level below 10 g/dL after hip fracture surgery.
Intervention: Patients were randomly assigned to a liberal transfusion strategy (a Hb threshold of 10 g/dL) or a restrictive transfusion strategy (anemia symptoms or at physician discretion for a Hb level less than 8 g/dL).
Primary Outcome: Mortality or inability to walk across a room without human assistance on a 60 day follow-up.
Results: Primary outcome rates were 35.2% in the liberal transfusion strategy group and 34.7% in the restrictive transfusion strategy group. Rates of complications were similar in the two groups.
Conclusion: A liberal transfusion strategy did not reduce mortality rates or the inability to walk independently on 60 day follow-up compared to a restrictive transfusion strategy in elderly patients with high cardiovascular risk factors after hip surgery.
Coagulation Factors

Table 39. Coagulation Factor Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen plasma (FP)</td>
<td>Depletion of multiple coagulation factors (e.g. sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose</td>
</tr>
<tr>
<td>Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII)</td>
<td>Factor VIII deficiency</td>
</tr>
<tr>
<td></td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td></td>
<td>Hypofibrinogemia</td>
</tr>
<tr>
<td>Humate P</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>Factor VIII concentrate</td>
<td>Factor VIII deficiency (Hemophilia A)</td>
</tr>
<tr>
<td>Factor IX concentrate</td>
<td>Factor IX deficiency (Hemophilia B)</td>
</tr>
<tr>
<td>Recombinant VIIa</td>
<td>Factor VII deficiency with bleeding, Hemophilia A or B with inhibitors</td>
</tr>
<tr>
<td>Prothrombin complex (Octaplex®)</td>
<td>Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or in patient requiring urgent (&lt;6 h) surgical procedure</td>
</tr>
</tbody>
</table>

Acute Blood Transfusion Reactions

IMMUNE

Acute Hemolytic Transfusion Reactions
- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation, occurs immediately after transfusion
- most commonly due to incorrect patient identification
- risk per unit of blood is <1 in 40,000
- presentation: fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

Febrile Nonhemolytic Transfusion Reactions
- due to alloantibodies to WBC, platelets or other donor plasma antigens and release of cytokines from blood product cells
- occurs within 0-6 h of transfusion
- risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <38°C, continue with transfusion but decrease rate and give antipyretics
  - if temperature >38°C, stop transfusion, give antipyretics and anti-histamine

Allergic Nonhemolytic Transfusion Reactions
- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1 in 100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema, and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenhydramine, steroids, epinephrine, IV fluids, and bronchodilators

Transfusion-Related Acute Lung Injury
- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - insidious, acute onset of pulmonary insufficiency
  - profound hypoxemia (PaO2/FiO2 <300 mmHg)
  - bilateral pulmonary edema on CXR
  - pulmonary artery wedge pressure <18 mmHg
  - no clinical evidence of left atrial HTN
- pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
- typically occurs 2-4 h post transfusion and resolves in 24-72 h
- risk per unit of blood is 1:10,000
  - is currently the leading cause of transfusion-related morbidity and mortality
- treatment: supportive therapy (oxygen)
  - inform blood bank; patient and donor testing will be arranged

DDx of Post-Transfusion Fever
- Acute hemolytic transfusion reaction
- Febrile non-hemolytic transfusion reaction
- Bacterial contamination
- Allergy

DDx of Post-Transfusion Dyspnea
- Transfusion-associated circulatory overload (TACO)
- Transfusion-related acute lung injury (TRALI)
- Allergy (bronchospasm/anaphylaxis)
NONIMMUNE

Transfusion-Associated Circulatory Overload
- due to impaired cardiac function and/or excessive rapid transfusion
- presentation: dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung, and increased venous pressure
- incidence: 1 in 700 and is becoming more common
- treatment: transfuse at lower rate, give diuretics and oxygen

Bacterial Infection
- Gram positive: S. aureus, S. epidermidis, Bacillus cereus
- Gram negative: Klebsiella, Serratia, Pseudomonas, Yersinia
- overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids

Hyperkalemia
- due to K+ release from stored RBC
- risk increases with storage time and if blood is irradiated and risk decreases
- if given fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP13

Citrate Toxicity
- occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca2+ and causes signs and symptoms of hypocalcemia
- treatment: IV calcium gluconate (10 mL of 10%) for every 2 units of blood

Dilutional Coagulopathy
- occurs with massive transfusion (>10 units)
- pRBC contains no clotting factors, fibrinogen, cryoprecipitate, or platelets
- treatment: FP, platelets, and cryoprecipitate

Delayed Blood Transfusion Reactions

IMMUNE

Delayed Hemolytic
- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, Kidd, and MNS
- titre of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
- occurs 5-7 d after transfusion
- presentation: anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion

Transfusion-Associated Graft Vs. Host Disease
- transfused T-lymphocytes recognize and react against “host” (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- may occur in immunocompetent individuals in setting of a designated transfusion from a related donor (decreased incidence with irradiated blood)
- presentation: fever, diarrhea, liver function abnormalities, and pancytopenia
- can be prevented by giving irradiated blood products

NONIMMUNE

Iron Overload
- due to repeated transfusions over long period of time (e.g. β-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if not longer requiring blood transfusion and not anemic

Viral Infection Risk
- HBV <1 in 153,000
- Human T-lymphotropic virus (HTLV) <1 in 4,300,000
- HCV <1 in 2,300,000
- HIV <1 in 7,000,000
- other infections include EBV, CMV, WNV (West Nile virus)
Common Medications

Antiplatelet Therapy

- see Figure 11a, Platelet Activation Cascade, H26

![Image of mechanism of action of antiplatelet therapy]

**Figure 15. Mechanisms of action of antiplatelet therapy**

**Table 40. Antiplatelet Therapy**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin® (ASA)</strong></td>
<td>Irreversibly acetylates COX, inhibiting TXA2 synthesis, thus inhibiting platelet aggregation</td>
<td>Single loading 200-300 mg PO, followed by dose of 75-190 mg PO daily</td>
<td>Onset: 5-30 min Peak: 0.25-3 h Duration: 3-6 h</td>
<td>GI ulcer/bleeding Tinnitus Bronchospasm Angioedema Reye’s syndrome in pediatric patients</td>
</tr>
<tr>
<td><strong>Aggrenox®</strong> (ASA + Dipyridamole)</td>
<td>Dipyridamole increases intracellular cAMP levels, which inhibits TXA2 synthesis, leading to decreased platelet aggregation</td>
<td>1 capsule PO bid Peak: 75 min</td>
<td>Headache Dyspepsia N/V Abdominal pain Cardiac failure Hemorrhoids</td>
<td>More effective than ASA in secondary prevention of stroke Dipyridamole potentiates antiplatelet action of ASA</td>
</tr>
<tr>
<td><strong>Clopidogrel (Plavix®)</strong></td>
<td>Inhibit ADP binding to platelets, thus decreased platelet aggregation</td>
<td>75-300 mg PO daily Onset: 2 h Peak: 1 h</td>
<td>URI Chest pain Headache Flu-like syndrome Depression UTI GI hemorrhage Pancytopenia May cause TTP</td>
<td>Prevention of cardiovascular events in high-risk patients CYP2C19 poor metabolizers have diminished response to clopidogrel Caution with hepatic/renal impairment</td>
</tr>
</tbody>
</table>

**Glycoprotein IIb/IIIa Inhibitors (Reopro®, abciximab, integrilin®)**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocking GP IIb/IIIa receptor inhibiting fibrinogen and vWF binding, leading to decreased platelet aggregation</td>
<td>Variable IV</td>
<td>Variable</td>
<td>Hypotension Back pain N/V Chest pain Abdominal pain Thrombocytopenia</td>
<td>Used most commonly in cardiac catheterization Contraindicated in PUD Monitoring aPTT/activated clotting time</td>
</tr>
</tbody>
</table>
Anticoagulant Therapy

Table 41. Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Reversing Agent</th>
<th>Monitoring</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>As per hospital nomogram</td>
<td>Onset: 20-60 min Peak: 2-4 h</td>
<td>Protamine sulphate</td>
<td>aPTT (intrinsic pathway), UFH (anti-Xa) levels</td>
<td>Hemorrhage HIT Increased liver enzymes</td>
<td>Pregnancy: safe (does not cross placenta)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Individualized dosing by monitoring PT/INR PO</td>
<td>Onset: 26-48 h Peak: 1.5-3 d</td>
<td>IV vitamin K PCC FFP</td>
<td>PT/INR maintain 2-3 (2.5-3.5 for mechanical values)</td>
<td>Hemorrhage Cholestrol embolism syndrome Intraocular hemorrhage</td>
<td>Pregnancy: not used, can cross placenta (teratogenic)</td>
</tr>
<tr>
<td>LMWH (enoxaparin, dalteparin, tinzaparin)</td>
<td>Inhibits FXa Variable SC/IV</td>
<td>Onset: 3-5 h Peak: 3-5 h Duration: 12 h</td>
<td>Partial reversibility with protamine sulphate</td>
<td>FXa in pediatrics, pregnancy and weight &gt; 150 kg</td>
<td>Hemorrhage Fever Increased liver enzymes &lt;1% HIT</td>
<td>Increased bioavailability than heparin Can accumulate in patients low CrCl (&lt; 30)</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Selective inhibitor of FXa Variable SC daily</td>
<td>Onset: 2 h Peak: 2-3 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Anemia Fever Nausea Rash</td>
<td>Heparin analogue Contraindicated in renal failure</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-FXa PO</td>
<td>Peak: 2-4 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Syncope GI hemorrhage</td>
<td>Only indicated in treatment of acute VTE (not in cancer patients), and thromboprophylaxis in orthopedic patients</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Direct thrombin inhibitor Variable IV</td>
<td>Onset: 5-10 min Duration: 2D-40 min</td>
<td>Not reversible</td>
<td>aPTT</td>
<td>Dyspnea Hypotension Fever</td>
<td>Indicated for HIT, renal failure, unstable patients</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor 150 mg PO bid</td>
<td>Peak: 1 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Gl upset Dyspepsia</td>
<td>Contraindicated in renal failure, cancer patients, mechanical heart valves</td>
</tr>
</tbody>
</table>

Contraindications:
- LMWH: Contraindicated in renal failure, pregnancy, placenta (teratogenic)
- Dabigatran: Contraindicated in renal failure, cancer patients, mechanical heart valves

Adverse Reactions of Heparin
- hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- heparin-induced thrombocytopenia: associated with venous or arterial thrombosis (see Table 23, H29)
- osteoporosis: with long-term use

Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)
- increased bioavailability compared to normal heparin
- increased duration of action
- SC route of administration
- do not need to monitor aPTT
- adverse reactions less common than UFH
- patients with renal failure (CrCl <30) can accumulate LMWH, therefore must adjust dose
- only partially reversible with protamine sulphate

Table 42. Recommended Therapeutic INR Ranges of Common Indications for Oral Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Most cases of thrombosis with antiphospholipid antibody syndrome</td>
<td></td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td></td>
</tr>
<tr>
<td>AMI (to prevent systemic embolism)</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Bileaflet mechanical valve in aortic position</td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthetic mitral valves (high risk)</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Prophylaxis of recurrent myocardial infarction</td>
<td></td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction
Table 43. Recommended Management of a Supratherapeutic INR

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding Present</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;Therapeutic to 4.5</td>
<td>No</td>
<td>Lower warfarin dose OR Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range OR No dose reduction needed if INR is minimally prolonged</td>
</tr>
<tr>
<td>&gt;4.5 to 10.0</td>
<td>No</td>
<td>Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range OR Omit a dose and administer 1 to 2.5 mg oral vit K in patients with increased risk of bleeding</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>No</td>
<td>Hold warfarin and administer 5 to 10 mg oral vit K; monitor INR more frequently and administer more vit K as needed; resume warfarin at a lower dose when INR is in therapeutic range</td>
</tr>
<tr>
<td>Any</td>
<td>Serious or life threatening</td>
<td>Hold warfarin and administer 10 mg vit K by slow IV infusion; supplement with four-factor prothrombin complex concentrate; monitor and repeat as needed</td>
</tr>
</tbody>
</table>


Chemotherapeutic and Biologic Agents Used in Oncology

Table 44. Selected Chemotherapeutic and Biologic Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism of Action or Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating Agent</td>
<td>chlorambucil, cyclophosphamide, melphalan (nitrogen mustards)</td>
<td>Damage DNA via alkylation of base pairs Leads to cross-linking of bases, abnormal base-pairing, DNA breakage</td>
</tr>
<tr>
<td></td>
<td>carboplatin, cisplatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dacarbazine, procarbazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>busulfan</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>methotrexate (follic acid antagonist)</td>
<td>Inhibit DNA synthesis</td>
</tr>
<tr>
<td></td>
<td>6-mercaptopurine, fludarabine (purine antagonist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-fluorouracil (5-FU) (pyrimidine antagonist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hydroxyurea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cytarabine</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>adriamycin (anthracycline)</td>
<td>Interfere with DNA and RNA synthesis</td>
</tr>
<tr>
<td></td>
<td>bleomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mitomycin C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>paclitaxel</td>
<td>Stabilize microtubules against breakdown once cell division complete</td>
</tr>
<tr>
<td></td>
<td>docetaxel</td>
<td></td>
</tr>
<tr>
<td>Vinca-alkaloids</td>
<td>vinblastine</td>
<td>Inhibit microtubule assembly (mitotic spindles), blocking cell division</td>
</tr>
<tr>
<td></td>
<td>vincristine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>vinorelbine</td>
<td></td>
</tr>
<tr>
<td>Topoisomerase Inhibitors</td>
<td>irinotecan, topotecan (topo I)</td>
<td>Interfere with DNA unwinding necessary for normal replication and transcription</td>
</tr>
<tr>
<td></td>
<td>etoposide (topo II)</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>prednisone</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>dexamethasone</td>
<td></td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>trastuzumab (Herceptin®)</td>
<td>HER2</td>
</tr>
<tr>
<td></td>
<td>bevacizumab (Avastin®)</td>
<td>VEGF</td>
</tr>
<tr>
<td></td>
<td>rituximab (Rituxan®)</td>
<td>CD20</td>
</tr>
<tr>
<td></td>
<td>cetuximab (Erbitux®)</td>
<td>EGFR</td>
</tr>
<tr>
<td>Small Molecule Inhibitors</td>
<td>imatinib mesylate (Gleevec®)</td>
<td>Bcr-Abl</td>
</tr>
<tr>
<td></td>
<td>dasatinib</td>
<td>Bcr-Abl</td>
</tr>
<tr>
<td></td>
<td>nilotinib</td>
<td>Bcr-Abl</td>
</tr>
<tr>
<td></td>
<td>erlotinib (Tarceva®)</td>
<td>EGFR</td>
</tr>
<tr>
<td></td>
<td>gefitinib (Iressa®)</td>
<td>EGFR</td>
</tr>
<tr>
<td></td>
<td>bortezomib (Velcade®)</td>
<td>26S proteasome</td>
</tr>
<tr>
<td></td>
<td>sunitinib (Sutent®)</td>
<td>VEGFR, PDGFR</td>
</tr>
<tr>
<td>Trial</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>AZA-001</td>
<td><em>Lancet Oncol</em> 2009; 10:223-32</td>
<td>Azacitidine increases overall survival in higher-risk myelodysplastic syndrome than conventional care</td>
</tr>
<tr>
<td>CHOP</td>
<td><em>NEJM</em> 1993; 328:1002-6</td>
<td>In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival; CHOP is the standard for advanced NHL</td>
</tr>
<tr>
<td>CLL8</td>
<td><em>Lancet</em> 2010; 376:1164-74</td>
<td>Rituximab plus fludarabine and cyclophosphamide (FCR) improves progression-free and overall survival compared with fludarabine and cyclophosphamide alone (FC) in the treatment of CLL</td>
</tr>
<tr>
<td>CLOT</td>
<td><em>NEJM</em> 2003; 349:146-53</td>
<td>In patients with cancer and acute venous thromboembolism, LWMH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding</td>
</tr>
<tr>
<td>CML: Imatinib vs. IFN + Cytarabine</td>
<td><em>NEJM</em> 2003; 349:994-1004</td>
<td>In patients with chronic-phase CML, imatinib was more effective than IFNα + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis</td>
</tr>
<tr>
<td>CYTO-PV</td>
<td><em>NEJM</em> 2013; 368(1), 22-33</td>
<td>In patients with polycythemia vera, a hematocrit target of &lt;0.45 for cytoreductive therapy is associated with prevention of thrombotic complications</td>
</tr>
<tr>
<td>Dabigatran vs. Warfarin in VTE</td>
<td><em>NEJM</em> 2009; 361:2342-52</td>
<td>In the treatment of venous thromboembolism, dabigatran is as effective as warfarin and also has a similar safety profile; note: many problems in the trial, making it less pivotal in having drug approval</td>
</tr>
<tr>
<td>Dose of Platelet Transfusion</td>
<td><em>NEJM</em> 2010; 392:609-13</td>
<td>Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions but not incidence of bleeding in patients with hypoproliferative thrombocytopenia</td>
</tr>
<tr>
<td>ESPIRIT</td>
<td><em>Lancet</em> 2008; 367:1665-73</td>
<td>ASA plus dipyridamole is recommended over ASA alone as antithrombotic therapy after cerebral ischemia of arterial origin</td>
</tr>
<tr>
<td>Hodgkin Lymphoma: ABVD vs. MOPP</td>
<td><em>NEJM</em> 1992; 327:1478-84</td>
<td>In Hodgkin lymphoma, ABVD regimen has equal failure-free and overall survival to MOPP + ABVD but less myelotoxicity; ABVD is standard chemotherapy for Hodgkin lymphoma</td>
</tr>
<tr>
<td>ITP: Dexamethasone</td>
<td><em>NEJM</em> 2003; 349:831-6</td>
<td>A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>MInT Group</td>
<td><em>Lancet</em> 2011; 12:1013-1022</td>
<td>Rituximab added to CHOP-like chemotherapy improved long-term outcomes for young patients with good-progression DLBCL</td>
</tr>
<tr>
<td>MSH</td>
<td><em>NEJM</em> 1995; 332:1317-22</td>
<td>Hydroxyurea is effective in reduction of complications and clinical manifestations of sickle cell disease</td>
</tr>
<tr>
<td>Platelet Transfusion Threshold</td>
<td><em>NEJM</em> 1997; 337:1870-5</td>
<td>The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10; use of the lower threshold reduced platelet usage by 21.5%</td>
</tr>
<tr>
<td>PT1</td>
<td><em>NEJM</em> 2005; 353:85-92</td>
<td>Hydroxyurea plus low-dose ASA is superior to anagrelide plus low-dose ASA for patients with essential thrombocythemia at high risk for vascular events</td>
</tr>
<tr>
<td>R-CHOP</td>
<td><em>NEJM</em> 2002; 346:235-42</td>
<td>Addition of rituximab to CHOP increases complete response rate and prolongs event-free survival and overall survival in elderly with DLBCL</td>
</tr>
<tr>
<td>StIL</td>
<td><em>Lancet</em> 2013; 381(9873):1203-10</td>
<td>Bendamustine plus rituximab is superior to R-CHOP in terms of progression-free survival and fewer toxic effects in patients with previously untreated indolent lymphoma</td>
</tr>
<tr>
<td>Therapeutic Platelet Transfusion</td>
<td><em>Lancet</em> 2012; 380:1309-16</td>
<td>Therapeutic platelet transfusions (when bleeding occurs) may be used if severe bleeding can be identified early in autologous stem-cell transplant patients; prophylactic transfusion (when platelets &lt;10) should remain standard of care in AML patients</td>
</tr>
<tr>
<td>TRICC</td>
<td><em>NEJM</em> 1999; 340:409-17</td>
<td>A restrictive strategy of red-cell transfusion (when Hb &lt;70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb &lt;100) in ICU patients; one possible exception is patients with an acute MI or unstable angina</td>
</tr>
<tr>
<td>VISTA</td>
<td><em>JCO</em> 2010; 28:2255-66</td>
<td>Bortezomib plus melphalan and prednisone (MPV) is superior to melphalan and prednisone (MP) in overall survival of non-transplant-eligible multiple myeloma patients</td>
</tr>
</tbody>
</table>
Infectious Diseases

Julie Caron, Lucas Djelic, and Sameer Rawal, chapter editors
Amanda Huynh, Jessica Huynh, and Vahagn Karapetyan, associate editors
Tina Hu, EBM editor
Dr. Andrea Boggild, Dr. Andrew Morris, Dr. Andrea Page, Dr. Susan Poutanen,
and Dr. Darrell Tan, staff editors

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Acronyms

Bacteriology

**Bacteria Basics**
- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on their cell wall
  - Gram positive (GP): thick, rigid layer of peptidoglycan
  - Gram negative (GN): thin peptidoglycan layer + thicker outer membrane composed of lipoproteins and lipopolysaccharides
  - clinical significance: GN thick outer membrane makes it resistant to penicillin's mechanism of action
- AFB: high myclic acid content in cell wall, "acid fast" as washout phase of Gram stain is ineffective, e.g. *Mycobacteria, Nocardia*
- "atypical" bacteria: not seen on Gram stain and difficult to culture
  - obligate intracellular bacteria: e.g. *Mycoplasma*
  - spirochetes: e.g. *Treponema pallidum*
- *O₂* can be either vital or detrimental to growth
  - obligate aerobes: require *O₂*
  - obligate anaerobes: require environment without *O₂*
  - facultative anaerobes: can survive in environments with or without *O₂*

**Mechanisms of Bacterial Disease**
1. adherence to and colonization of skin or mucous membranes
   - e.g. fimbrilation (pill) microfilaments extending through the cell wall – like burrs sticking to your clothes, they attach to epithelial cells e.g. *E. coli* in the urinary tract
2. invasion or crossing normal epithelial barriers
   - evasion of host defense system through inhibition of:
     - phagocytic uptake via polysaccharide capsule (*S. pneumoniae, N. meningitidis, H. influenzae*)
     - or surface proteins (*Staphylococcus, Streptococcus*)
3. toxin production
   - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (e.g. *Clostridium*)
   - endotoxins are structural components of GN bacterial cell wall, and may be shed by live cells or released during cell lysis
4. intracellular growth
   - obligate intracellular: *Rickettsia* and *Chlamydia*
   - facultative intracellular: *Salmonella, Neisseria, Brucella, Mycobacteria, Listeria, Legionella*
5. biofilm
   - an extracellular polysaccharide network forming mesh around the bacteria (e.g. *S. epidermidis*) which can coat prosthetic devices like IV catheters

**Figure 1. Bacteria morphology**

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Table 1. Common Bacteria

<table>
<thead>
<tr>
<th>Gram-Positive Bacteria</th>
<th>Gram-Negative Bacteria</th>
<th>Not Seen on Gram Stain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>B. anthracis</td>
<td>Neisseria</td>
</tr>
<tr>
<td>S. aureus</td>
<td>S. saprophyticus</td>
<td>N. meningitidis</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>N. gonorrheae</td>
<td>Moraxella</td>
</tr>
<tr>
<td>Streptococcus</td>
<td></td>
<td>M. catarrhalis</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. pyogenes (GAS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S. agalactiae (GBS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. faecalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peptostreptococcus</td>
<td>Clostridium</td>
<td>Bacteroides</td>
</tr>
<tr>
<td></td>
<td>C. difficile, C. tetani, C. botulinum, C. perfringens</td>
<td>B. fragilis</td>
</tr>
</tbody>
</table>

Table 2. Commensal Flora

<table>
<thead>
<tr>
<th>Site</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Coagulase-negative staphylococci, Corynebacteria, Propionibacterium acnes, Bacillus, S. aureus</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Viridans group streptococci, Haemophilus, Neisseria, anaerobes (Peptostreptococcus, Bacteroides, Veillonella, Fusobacterium, Actinomyces, Prevotella)</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>E. coli, anaerobes (low numbers)</td>
</tr>
<tr>
<td>Colon</td>
<td>E. coli, Klebsiella, Enterobacter, Enterococcus, anaerobes (Bacteroides, Peptostreptococcus, Clostridium)</td>
</tr>
<tr>
<td>Vagina</td>
<td>Lactobacillus acidophilus, Viridans group streptococci, coagulase-negative staphylococci, facultative GN bacilli, anaerobes</td>
</tr>
</tbody>
</table>

Figure 2. Laboratory identification of bacterial species
# Virology

## Viral Basics
- Viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - Infect cells and use host metabolic machinery to replicate
  - Nucleic acid can be double stranded (ds) or single stranded (ss)
  - Can be enveloped or naked
- Virions are mature virus particles that can be released into the extracellular environment
- Host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

## Viral Disease Patterns
1. Acute infections (e.g. adenovirus)
   - Host cells are lysed in the process of virion release
   - Some produce acute infections with late sequelae (e.g. measles virus → subacute sclerosing panencephalitis)
2. Chronic infections (>6 mo): (e.g. HBV, HIV)
   - Host cell machinery is used to produce and chronically release virions
3. Latent infections
   - Viral genome remains latent in host cell nucleus
   - Can reactivate (e.g. HSV, VZV)

## Table 3. Common Viruses

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Enveloped</th>
<th>Virus Family</th>
<th>Major Viruses</th>
<th>Medical Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>N</td>
<td>Adenoviridae</td>
<td>Adenovirus</td>
<td>URTI, Conjunctivitis, Gastroenteritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Papillomaviridae</td>
<td>HPV1, 4, HPV6, 11, HPV16, 18, etc.</td>
<td>Plantar warts, Genital warts, Cervical/anal dysplasia and cancer</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV1=HSV1, HHV2=HSV2, HHV3=VZV, HHV4=EBV, HHV5=CMV, HHV6=KSHV</td>
<td>Oral, ocular, and genital herpes, encephalitis, Chicken pox, shingles, Retinitis, pneumonitis, hepatitis, encephalitis, Rosacea, Kaposis’s sarcoma, multicentric Castleman’s disease, body cavity lymphoma</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Polyomaviridae</td>
<td>JC virus</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Hepadnaviridae</td>
<td>Hepatitis B</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poxviridae</td>
<td>Variola</td>
<td>Smallpox</td>
</tr>
<tr>
<td>ssDNA</td>
<td>N</td>
<td>Paroviridae</td>
<td>Parovirus B19</td>
<td>Erythema infectiosum (Fifth disease)</td>
</tr>
<tr>
<td>(+)ssRNA</td>
<td>N</td>
<td>Caliciviridae</td>
<td>Norwalk, Hepatitis E</td>
<td>Gastroenteritis, Acute hepatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Picornaviridae</td>
<td>Poliovirus, Echovirus, Rhinovirus, Coxsackie virus</td>
<td>Poliomyelitis, URTIs, viral meningitis, Hand-foot-and-mouth, viral meningitis, myocarditis, Acute hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Coronaviridae</td>
<td>Coronavirus</td>
<td>URTIs, SARS</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Flaviviridae</td>
<td>Yellow fever, Dengue fever, Hepatitis C, West Nile</td>
<td>Yellow fever, Dengue fever, Hepatitis, Encephalitis, flaccid paralysis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Togaviridae</td>
<td>Rubella</td>
<td>Rubella (German measles)</td>
</tr>
<tr>
<td>(+)ssRNA-RT</td>
<td>Y</td>
<td>Retroviridae</td>
<td>HIV, HTLV-1</td>
<td>AIDS, T-cell leukemia and lymphoma</td>
</tr>
<tr>
<td>(-)ssRNA</td>
<td>Y</td>
<td>Arenaviridae</td>
<td>Lassa fever</td>
<td>Lassa fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Filoviridae</td>
<td>Ebola, Marburg</td>
<td>Hemorrhagic fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Orthomyxoviridae</td>
<td>Influenza A, B, C</td>
<td>Influenza</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>Measles, Mumps, Parainfluenza, RSV</td>
<td>Measles, Mumps, URTIs, croup, bronchiolitis, Bronchiolitis, pneumonia</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Rhabdoviridae</td>
<td>Rabies</td>
<td>Rabies</td>
</tr>
<tr>
<td>dsRNA</td>
<td>N</td>
<td>Reoviridae</td>
<td>Rotavirus</td>
<td>Gastroenteritis</td>
</tr>
</tbody>
</table>

Note: __viridae = family, __virus = genus, # = species (e.g. Retroviridae HIV-2)
*Roseolovirus, Herpes lymphotropic virus

Figure 3. Virus morphology
Mycology

Fungal Basics
- fungi are eukaryotic organisms, they can have the following morphologies
  1. yeast (unicellular)
  2. molds (also known as filamentous fungi) (multicellular with hyphae)
  3. dimorphic fungi (found as mold at room temperature but grow as yeast-like forms at body temperature)

Table 4. Membrane and Cell Wall Compositions

<table>
<thead>
<tr>
<th>Membrane Sterol</th>
<th>Cell Wall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Peptidoglycan</td>
</tr>
<tr>
<td>Human Cell</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Fungi</td>
<td>Ergosterol, Chitin</td>
</tr>
</tbody>
</table>

Mechanisms of Fungal Disease
- primary fungal infection by
  - overgrowth of normal flora (e.g. Candida species)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion aflatoxins)
- allergic reactions to fungi (e.g. bronchopulmonary aspergillosis)

Parasitology

Parasite Basics
- parasite: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycles require more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed to the larval stage
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see Tables 26 and 27 for examples of clinically important parasites

Table 5. Differences Between Protozoa and Helminths

<table>
<thead>
<tr>
<th>Protozoa</th>
<th>Helminths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unicellular</td>
<td>Multicellular</td>
</tr>
<tr>
<td>Motile trophozoite → inactive</td>
<td>Adult → egg → larva</td>
</tr>
<tr>
<td>Multiplication</td>
<td>No multiplication</td>
</tr>
<tr>
<td>± Eosinophilia</td>
<td>Eosinophilia (proportional to extent of tissue invasion)*</td>
</tr>
<tr>
<td>Indefinite life span</td>
<td>Definite life span</td>
</tr>
</tbody>
</table>

*Adult ascari (roundworm) does not cause eosinophilia

Characteristics of Parasitic Disease
- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic infection

Mechanisms of Parasitic Disease
1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B12 deficiency in diphyllobothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
  - acute hypersensitivity (e.g. pneumonitis in Loeffler’s syndrome)
  - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
  - cytokine-mediated (systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
  - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
  - immune complex (e.g. nephritis of malaria, schistosomiasis)
Transmission of Infectious Diseases

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mode of Transmission</th>
<th>Examples</th>
<th>Preventative Measure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Direct physical contact, or indirect contact with a fomite</td>
<td>Person-to-person (MRSA) Sexual (N. gonorrhoeae, C. trachomatis, HSV, HIV) Blood-borne (HIV, HBV, HCV)</td>
<td>For patients in health care facilities: Contact precautions (see Prevention of Infectious Diseases) Barrier precautions Safe needlestick/sharp practices</td>
</tr>
<tr>
<td>Droplet/Contact</td>
<td>Respiratory droplets (&gt;5 µm) can be projected short distances (&lt;2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids</td>
<td>Influenza, mumps N. meningitidis, Bordetella pertussis</td>
<td>For patients in health care facilities: Contact/droplet precautions (see Prevention of Infectious Diseases)</td>
</tr>
<tr>
<td>Airborne</td>
<td>Airborne droplet nuclei (&lt;5 µm) can remain infectious over time and distance</td>
<td>M. tuberculosis, V2(1), measles</td>
<td>For patients in health care facilities: Airborne precautions (see Prevention of Infectious Diseases)</td>
</tr>
<tr>
<td>Food/Waterborne</td>
<td>Ingestion of contaminated food or water</td>
<td>V. cholerae, Salmonella, HAV, HEV</td>
<td>Prophylactic vaccinations where available Ensure clean food/water supply For patients in health care facilities: Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers</td>
</tr>
<tr>
<td>Zoonotic</td>
<td>Disease transmission from animals to humans either directly or via an insect vector</td>
<td>Animals (rabies, Q fever) Arthropods (malaria, Lyme disease)</td>
<td>Prophylactic medications, vaccinations Protective clothing, insect repellent, mosquito nets, tick inspection</td>
</tr>
<tr>
<td>Vertical</td>
<td>Spread of disease from parent to offspring</td>
<td>Congenital syndromes (TORCH infections) Perinatal (HIV, HBV, GBS)</td>
<td>Prenatal screening Prophylactic treatment</td>
</tr>
</tbody>
</table>

*see Prevention of Infectious Diseases for further detail

Prevention of Infectious Diseases

Overview
- efforts to control the spread of infectious disease involves infection control and prevention measures in health care settings and public health measures outside of health care settings

Infection Control and Prevention Measures
1. surveillance for important nosocomial infections or problem organisms (such as: surgical site infections, vascular access-related infections, C. difficile infections, colonization or infections due to antimicrobial resistant organisms e.g. methicillin-resistant S. aureus). (see Population and Community Health, PH19 for a definition of active vs. passive surveillance)
2. routine practices (also known as standard precautions) used for all patients
   - perform hand hygiene before and after seeing patient or patient environment contact, before aseptic procedures, and after body fluid exposure
   - use gloves for any encounter with body fluids
   - wear eye protection, mask, and gown for any procedures likely to generate splashes of body fluids
   - do not recap sharps by hand and dispose of sharps in puncture-resistant container near point-of-use
   - use mouthpieces for resuscitator bags instead of using mouth-to-mouth resuscitation
   - discard soiled waste properly
3. additional precautions used for various syndromes or known infectious diseases
   - contact precautions (private room, gown, gloves to be used routinely) (e.g. used for patients with C. difficile)
   - droplet/contact precautions (private room, gown, gloves, eye protection, fluid-resistant mask) (e.g. used for influenza, meningitis due to Neisseria meningitidis)
   - airborne precautions (negative-pressure private room with door closed, fit-tested N95 respirator) (e.g. used for TB, measles, VZV)

Study: RCT stopped after an interim analysis.
Population: 43 patients at least 18 yr of age, with a life expectancy of at least 3 mo, and a relapse of C. difficile after at least one course of adequate antibiotic therapy (≥10 d of vancomycin at a dose of ≥125 mg q6h or ≥10 d of metronidazole at a dose of 500 mg q8h).
Primary Outcome: Resolution of diarrhea associated with C. difficile infection without relapse after 10 wk.
Results: 87% of patients in the group with duodenal infusion of donor feces had a resolution of C. difficile-associated diarrhea after the first infusion. 31% of patients receiving vancomycin with bowel lavage had a resolution of C difficile-associated diarrhea. After the infusion, patients showed greater fecal bacterial diversity similar to healthy donors.
Conclusions: Infusion of donor feces was more effective for the treatment of recurrent C. difficile infection than the use of vancomycin alone or vancomycin with bowel lavage.
4. decolonization (e.g. topical and oral antimicrobials be used in an attempt to decolonize methicillin-resistant S. aureus [MRSA])
5. outbreak investigations (see Population and Community Health, PH19)

Public Health Measures
1. vaccination
2. post-exposure prophylaxis (e.g. use of immunoglobulin or vaccination post-exposure to infectious disease agents in an attempt to reduce the likelihood or severity of disease)
3. reportable diseases (e.g. list of reportable communicable diseases that physicians are legally required to report to local public health officials) (see Population and Community Health, PH25)
4. contact tracing (tracking of individuals who have been exposed to a person with a communicable disease during its period of communicability)
5. quarantine (restriction of the activities or well persons who have been exposed to a person with a communicable disease during its period of communicability to prevent disease transmission during the incubation period if infection should occur)
6. outbreak investigation (see Population and Community Health, PH19)

Nosocomial Infections

- definition: infections acquired >48 h after admission to a healthcare facility or within 30 d from discharge
- risk factors: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
- patients with nosocomial infections have higher mortality, longer hospital stays, and higher healthcare costs
- hand hygiene is an essential precaution

Table 7. Common Nosocomial Infectious Agents

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Characteristics</th>
<th>Manifestation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-Resistant Staphylococcus aureus (MRSA)</td>
<td>Gram-positive cocci</td>
<td>Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis</td>
<td>Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR</td>
<td>Contact precautions For infection: vancomycin or daptomycin or linezolid To decolonize: 2% chlorhexidine wash OD (+ rifampin + doxycycline + mupirocin cream bid to nares) x 7 d</td>
</tr>
<tr>
<td>Vancomycin-Resistant Enterococcus (VRE)</td>
<td>Majority are E. faecium Resistant if minimum inhibitory concentration of vancomycin is ≥32 μg/mL</td>
<td>Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis</td>
<td>Rectal or perirectal swab OR stool culture for colonization Culture of infected site</td>
<td>Contact precautions Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified</td>
</tr>
<tr>
<td>Clostridium difficile (C. difficile)</td>
<td>Releases exotoxins A and B Hypervirulent strain has been responsible for increase in incidence and severity Fever, nausea, abdominal pain Watery diarrhea ± occult blood Pseudomembranous colitis Severe: toxic megacolon Risk of bowel perforation Associated with antibiotic use Leukocytosis</td>
<td>Stool PCR Stool immunoassay for toxins A and B AXR (may see colonic dilatation) Sigmoidoscopy for pseudomembranes; avoid if known colonic dilatation</td>
<td></td>
<td>Contact precautions Stop culprit antibiotic therapy Supportive therapy (IV fluids) Mild-moderate disease: metronidazole PO/IV x 10-14 d Severe disease: vancomycin PO x 10-14 d Toxic megacolon: metronidazole IV + vancomycin PO (as above) and general surgery consult</td>
</tr>
<tr>
<td>Extended Spectrum β-Lactam Producers (ESBL producing E. coli, K. pneumoniae)</td>
<td>Resistant to most β-lactam producing antibiotics e.g. penicillins, aztreonam, and cephalosporins UTI Pulmonary infection Bacteremia Liver abscess in susceptible patients Meningitis</td>
<td>Blood, sputum, urine, or aspirated body fluid culture Imaging at infection site (CXR, CT, U/S)</td>
<td></td>
<td>Carbapenems or non-β-lactam antibiotics can be used for empiric therapy</td>
</tr>
</tbody>
</table>
Pneumonia

• see Pediatrics, P90
• see Family Medicine, FM18

Definition
• infection of the lung parenchyma

Etiology and Risk Factors
• impaired lung defenses
  ▪ poor cough/gag reflex (e.g. illness, drug-induced)
  ▪ impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  ▪ immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
• increased risk of aspiration
  ▪ impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia, mechanical obstruction)
• no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

Table 8. Common Organisms in Pneumonia

<table>
<thead>
<tr>
<th>Community Acquired</th>
<th>Nosocomial</th>
<th>Aspiration</th>
<th>HIV-associated</th>
<th>Alcoholic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>Enteric GNB (E. coli)</td>
<td>Oral anerobes (Bacteroides)</td>
<td>Pneumocystis jiroveci</td>
<td>Klebsiella</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>Pseudomonas aeruginosa</td>
<td>Enteric GNB (E. coli)</td>
<td>Fungi (Cryptococcus)</td>
<td>Enteric GNB</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>S. aureus (including MRSA)</td>
<td>S. aureus</td>
<td>Nocardia</td>
<td>S. aureus</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>Gastic contents (chemical pneumonitis)</td>
<td>GAS</td>
<td>CMV</td>
<td>Oral anerobes (aspiration)</td>
</tr>
<tr>
<td>GAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legionella pneumophila</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*See Pediatrics P90, Table 45 for Common Causes and Treatment of Pneumonia at Different Ages

Clinical Features
• cough (+ sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
• elderly often present atypically; altered LOC is sometimes the only sign
• evidence of consolidation (dullness to percussion, bronchial breath sounds, crackles)
• features of parapneumonic effusion (decreased air entry, dullness to percussion) (see Respirology, R21)
• complications: ARDS, lung abscess, parapneumonic effusion/empyema, pleuritis ± hemorrhage

Investigations
• pulse oximetry to assess severity of respiratory distress
• CBC and differential, electrolytes, urea, Cr, ABG (if respiratory distress), troponin/CK, LFTs, urinalysis
• sputum Gram stain/C&S, blood C&S, ± serology/viral detection, ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
• CXR±CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
• bronchoscopy ± washings for:
  ▪ (1) severely ill patients refractory to treatment or (2) immunocompromised patients

Treatment
• ABC, O2, IV fluids, consider salbutamol (nebulized or MDI)
• determine prognosis and need for hospitalization and antibiotics

When Klebsiella causes pneumonia; see red currant jelly sputum

Aspiration pneumonias more commonly manifest as infiltrates in the right middle or lower lobes due to the larger caliber and more vertical orientation of the right bronchus

Figure 6. Lobar, broncho, and interstitial pneumonia

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Criteria for Hospitalization

Table 9. CURB 65 Score – Pneumonia Clinical Prediction Tool

<table>
<thead>
<tr>
<th>Component</th>
<th>Measurement(s)</th>
<th>Points</th>
<th>Total Score</th>
<th>Mortality</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>Altered mental status</td>
<td>1</td>
<td>0-1</td>
<td>&lt;5%</td>
<td>Can treat as outpatient</td>
</tr>
<tr>
<td>Urea/BUN</td>
<td>Urea &gt; 7 mmol/L or BUN &gt; 20 mg/dL</td>
<td>1</td>
<td>2-3</td>
<td>5-15%</td>
<td>Consider hospitalization</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>&gt; 30 breaths/min</td>
<td>1</td>
<td>4-5</td>
<td>15-30%</td>
<td>Consider ICU</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Systolic &lt; 90 or diastolic &lt; 60 mmHg</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65 or older</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007

<table>
<thead>
<tr>
<th>Setting</th>
<th>Circumstances</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>Previously well</td>
<td>Macrolide¹ OR Doxycycline</td>
</tr>
<tr>
<td></td>
<td>No antibiotic use in last 3 mo</td>
<td>OR Respiratory fluoroquinolone³ + β-lactam⁴</td>
</tr>
<tr>
<td></td>
<td>Comorbidities²</td>
<td>OR (β-lactam⁴ + Macrolide¹)</td>
</tr>
<tr>
<td></td>
<td>Antibiotic use in last 3 mo (use different class)</td>
<td>OR Respiratory fluoroquinolone³ + β-lactam⁴</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inpatient</th>
<th>Ward</th>
<th>Respiratory fluoroquinolone³ + β-lactam⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU</td>
<td></td>
<td>(β-lactam⁴ + (Macrolide¹ OR Respiratory fluoroquinolone³))</td>
</tr>
</tbody>
</table>

1. Macrolide: azithromycin, clarithromycin, erythromycin
2. Comorbidities: chronic heart, lung, liver, or renal disease, DM, alcoholism, malignancy, asplenia, immunocompromised
3. Respiratory fluoroquinolone: moxifloxacin, gemifloxacin, levofloxacin
4. β-lactam: cefotaxime, ceftriaxone, ampicillin-sulbactam

Table 11. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

<table>
<thead>
<tr>
<th>Setting</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors for multidrug resistance (MDR) Early onset (&lt;5 d)</td>
<td>ceftriaxone OR levofloxacin, moxifloxacin, or ciprofloxacin OR ampicillin/sulbactam OR ertapenem</td>
</tr>
<tr>
<td>Late onset disease (&gt;5 d) or With risk factors for MDR:</td>
<td>antipseudomonal cefepime or ceftazidime</td>
</tr>
<tr>
<td>Antibiotic use in last 3 mo High frequency of antibiotic resistance in the community or in the specific hospital unit</td>
<td>OR OR antipseudomonal carbapenem (imipenem or meropenem) OR OR β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) PLUS OR antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) OR OR aminoglycoside (aminoglycoside, gentamicin, or tobramycin) PLUS OR MRSA linezolid or vancomycin PLUS OR for Legionella ensures regime includes either a macrolide or a fluoroquinolone</td>
</tr>
<tr>
<td>Hospitalization &gt;1 d in past 3 mo Residence in a nursing home or extended care facility Dialysis within 30 d Home wound care Family member with multidrug-resistant pathogen Immunocompromised disease and/or therapy</td>
<td></td>
</tr>
</tbody>
</table>

Note: Always use directed therapy against specific organism if one is found on culture (e.g. blood, sputum, etc.)

Prevention

- Vaccine for influenza A and B recommended annually for all ages
- Two pneumococcal polysaccharide vaccines available: 23 valent (indicated for all adults) and 13 valent (indicated for adults >50 yr)
- The CDC recommends giving Prevnar-13® to all adults at high risk for invasive pneumococcal disease (>65 yr, 19-64 with chronic disease, smokers, residents of long-term care facilities, Aboriginal peoples 50-64 yr)
### Influenza

**Definitions and Etiology**
- influenza viruses A and B
- influenza A further divided into subtypes based on envelope glycoproteins:
  - hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: human-origin A (H1N1) and B (H3N2) subtypes
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
  - outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift: abrupt, major changes due to mixing of two different viral strains from different hosts
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
  - antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

| Table 12. Difference Between Influenza Strains |
|-----------------|-----------------|
|                | Influenza A     | Influenza B     |
| Host(s)        | Humans, birds, mammals | Humans only |
| Antigenic drift| Yes, new strains | Yes, new strains |
| Antigenic shift | Yes, new subtypes | No |
| Epidemics      | Yes             | Yes             |
| Pandemics      | Yes             | No              |

**Clinical Features**
- incubation period 1-4 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, headache, fatigue) and respiratory symptoms (cough, dyspnea, pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, Guillain-Barré syndrome)

**Investigations**
- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for rapid antigen detection, DFA (Direct Fluorescent Antigen) detection, RT-PCR (gold standard)
- serology: rarely used for clinical management

**Treatment and Prevention**
- primarily supportive unless severe infection or high-risk of complications (e.g. elderly, pulmonary or cardiac disease)
- neuraminidase inhibitors: zanamivir (Relenza*) and oseltamivir (Tamiflu*) for treatment and prophylaxis against types A and B
  - decreases duration (by 1-2 d) and severity of symptoms if given within <48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- M2-inhibitors: amantidine/rimantidine for treatment and prophylaxis against type A only no longer recommended due to increased resistance
- vaccine for influenza A and B viruses is recommended annually for all ages
  - vaccine is reformulated each year to reflect circulating influenza A and B strains

### Cellulitis

**Definition**
- acute infection of the skin principally involving the dermis and subcutaneous tissue

**Etiology**
- common causative agents: S. aureus, β-hemolytic streptococci
- immunocompromised patients or water exposure: may also include GN rods and fungi
- risk factors:
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema diabetes, cracked skin in feet/toes (tinea pedis)

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*Vaccines for Preventing Influenza in Healthy Adults*

*Cochrane DB Syst Rev 2014;CD001269*

**Study:** Meta-analysis of 90 RCTs and quasi-RCTs evaluating influenza vaccines compared to placebo in healthy individuals aged 16-65 yr.

**Results:** The preventative effect of inactivated influenza vaccine on healthy adults is small: 40 people would need a vaccination to avoid one influenza-like illness and 71 people would need a vaccination to prevent one case of influenza. 15.6% of unvaccinated vs. 9.9% of vaccinated people developed influenza-like symptoms: of these participants, only 2.4% and 1.1%, respectively, developed laboratory-confirmed influenza. Vaccination had a modest effect on working days lost, but no effects on hospitalization or complications. The effectiveness of live aerosol vaccinations on healthy adults is similar to that of inactivated influenza vaccines: 46 people would need a vaccination to avoid one influenza-like illness.

**Conclusions:** Influenza vaccines have a very modest effect in reducing influenza-like illness and working days lost in the general population.
Clinical Features
• pain, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
• can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

Investigations
• CBC and differential, blood C&S if febrile
• skin swab ONLY if open wound with pus

Treatment
• antibiotics: cephalaxin (broader coverage if risk factors for GN rods)
• if extensive erythema or systemic symptoms, consider cefazolin IV
• limb rest and elevation may help reduce swelling

Necrotizing Fasciitis

Definition
• life- and limb-threatening infection of the deep fascia characterized by rapid spread

Etiology
• Two main forms
  ▪ Type I: polymicrobial infection – aerobes and anaerobes (e.g. S. aureus, Bacteroides, Enterobacteriaceae)
  ▪ Type II: monomicrobial infection with GAS

Clinical Features
• pain out of proportion to clinical findings and beyond border of erythema
• edema, ± crepitus (subcutaneous gas from anaerobes), ± fever
• infection spreads rapidly
• patients may rapidly become very sick (tachycardia, hypotension, lightheadedness)
• late findings
  ▪ skin turns dusky blue and black (secondary to thrombosis and necrosis)
  ▪ induration, formation of hemorrhagic bullae

Investigations
• a clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
• blood and tissue C&S
• serum CK (elevated CK usually means myonecrosis – a late sign)
• plain film x-ray (soft tissue gas may be visualized)
• surgical exploration for debridement of infected tissue

Treatment
• resuscitation with IV fluids
• emergency surgical debrideaments to confirm diagnosis and remove necrotic tissue (may require amputation)
• IV antibiotics
  ▪ unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin if MRSA is considered
  ▪ Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  ▪ Type II (monomicrobial): penicillin G + clindamycin IV
  ▪ with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIg

Gastrointestinal Infections

Acute Diarrhea
• see Gastroenterology, G15
• see Pediatrics, P35
• see Family Medicine, FM26

Epidemiology
• one of the top five leading causes of death worldwide, according to the World Health Organization
• significant morbidity in developed countries (over 900,000 hospitalizations in United States each year)
Definition
• passage of ≥3 loose or liquid stools/d OR >200 g stool/d for >2 d but ≤14 d

Approach to Acute Diarrhea
• rationale
  ▪ the vast majority of acute diarrhea is caused by infection
  ▪ in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
  ▪ investigations are costly and are necessary only in certain circumstances
• therefore, the evaluation of acute diarrhea involves:
  ▪ identifying characteristics of the illness or patient that warrant further investigation
  ▪ assessing volume status to determine appropriate method of rehydration
• see Figure 7

Physical Exam
• volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
• abdominal exam: pain, guarding, peritoneal signs

Treatment
• rehydration is mainstay of treatment
  ▪ oral rehydration therapy
  ▪ IV rehydration if oral intake insufficient to replace fluid loss
• antidiarrheal agents reduce duration of diarrhea: loperamide, bismuth salicylate
  ▪ delays excretion of causative pathogens
  ▪ contraindications: diarrhea with fever, bloody stool or diarrhea caused by Clostridium difficile
• antibiotic therapy is rarely indicated because:
  ▪ most acute diarrheal illness is viral and self-limited
  ▪ antibiotics can eradicate normal gut flora, predisposing patient to C. difficile infection
  ▪ antibiotics prolong the shedding of Salmonella and other causes of bacterial diarrhea
  ▪ in EHEC infection, antibiotics may increase the risk of HUS
  ▪ indications for antibiotic therapy are shown in Figure 7

Figure 7. Approach to acute diarrhea
# Table 13. Bacteria in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. cereus – Type A (emic)</td>
<td>Rice dishes</td>
<td>1-6 h</td>
<td>–</td>
<td>–</td>
<td>+ (&lt;12 h)</td>
<td>None</td>
</tr>
<tr>
<td>B. cereus – Type B (diarheal)</td>
<td>Meats, vegetables, dried beans, cereals</td>
<td>8-16 h</td>
<td>–</td>
<td>–</td>
<td>– (&lt;24 h)</td>
<td>None</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Uncooked meat, especially poultry</td>
<td>2-10 d</td>
<td>+ ±</td>
<td>± ± ± ±</td>
<td>± (&lt;1 wk)</td>
<td>Macrolide or fluoroquinolone if diarrhea &gt; 1 wk, bloody diarrhea, or immunocompromised</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Can be normally present in colon in small numbers (primary risk factor for disease is exposure to antitoxins)</td>
<td>Unclear</td>
<td>± ± ± ±</td>
<td>Variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>Contaminated food, especially meat and poultry</td>
<td>8-12 h</td>
<td>± ±</td>
<td>± ± ± ±</td>
<td>± (&lt;24 h)</td>
<td>None</td>
</tr>
<tr>
<td>Enteroinvasive E. coli (EIEC)</td>
<td>Contaminated food/water</td>
<td>1-3 d</td>
<td>+ ±</td>
<td>± ± ± ±</td>
<td>± (&lt;7d)</td>
<td>None</td>
</tr>
<tr>
<td>Enterotoxigenic E. coli (ETEC)</td>
<td>Contaminated food/water</td>
<td>1-3 d</td>
<td>– ±</td>
<td>± ± ± ±</td>
<td>± (&lt;3d)</td>
<td>Fluoroquinolone or azithromycin for moderate to severe symptoms</td>
</tr>
<tr>
<td>Enterohemorrhagic E. coli</td>
<td>Contamination of hamburger, raw milk, and drinking and recreational water</td>
<td>3-8 d</td>
<td>– ±</td>
<td>± ± ± ±</td>
<td>5-10d</td>
<td>None: antibiotics increase risk of HUS</td>
</tr>
<tr>
<td>Salmonella typhi S. paratyphi</td>
<td>Fecal-oral Contaminated food/water, travel to endemic area</td>
<td>10-14 d</td>
<td>+ ±</td>
<td>± ± ± ±</td>
<td>± (&lt;5-7d)</td>
<td>Shiga toxin production Monitor renal function: 10% develop HUS Antidiarrheals increase risk of HUS</td>
</tr>
<tr>
<td>Non-typhoidal Salmonellosis S. typhimurium, S. enteritidis</td>
<td>Contaminated food products, especially eggs, poultry, meat, milk</td>
<td>12-72 h</td>
<td>+ ±</td>
<td>± ± ± ±</td>
<td>± (&lt;3-7d)</td>
<td>Ciprofloxacin only in severe illness, extremes of age, joint protheses, valvular heart disease, severe atherosclerosis, cancer, uremia</td>
</tr>
<tr>
<td>Shigella dysenteriae</td>
<td>Fecal-oral Contaminated food/water</td>
<td>1-4 d</td>
<td>+ ±</td>
<td>± ± ± ±</td>
<td>± (&lt;1 wk)</td>
<td>Fluoroquinolone Very small inoculum needed for infection Complications include toxic megacolon, HUS Antidiarrheals may increase risk of toxic megacolon</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Unrefrigerated meat and dairy products (custard, pudding, potato salad, mayo)</td>
<td>2-4 h</td>
<td>– ±</td>
<td>± ± ± ±</td>
<td>± (&lt;1-2d)</td>
<td>None Heat-stable preformed exotoxin</td>
</tr>
<tr>
<td>Vibrio cholerae</td>
<td>Contaminated food/water, especially shellfish</td>
<td>1-3 d</td>
<td>– ±</td>
<td>± ± ± ±</td>
<td>± (&lt;3-7d)</td>
<td>Tetracycline or quinolones (ciprofloxacin) Massive watery diarrhea (1-3 L/d) Mortality &lt;1% with treatment</td>
</tr>
</tbody>
</table>
| Yersinia                        | Contaminated food Unpasteurized milk | 5 d        | + ±               | ± ± ± ±  | ± (<Up to 3 wk)       | Fluoroquinolone only for severe illness Majority of cases in children 1-4 yr Mesenteric adenitis and terminal ileitis can occur without diarrhea, mimicking appendicitis
**Traveler’s Diarrhea**

- see *Acute Diarrhea*, ID11

**Epidemiology**
- the most common illness to affect travelers
- up to 50% of travelers to developing countries affected in first 2 wk and 10-20% after returning home

**Etiology**
- bacterial (80-90%): *E. coli* most common (ETEC), *Campylobacter, Shigella, Salmonella, Vibrio* (non-cholera); wide regional variation (e.g. *Campylobacter* more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8%
- protozoal (rarely): *Giardia, Entamoeba histolytica, Cryptosporidium, Cyclospora* for ~10% in long-term travelers
- pathogen-negative traveler’s diarrhea common despite exhaustive microbiological workup

**Treatment**
- rehydration is the mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss use oral rehydration solutions (1 package in 1 L boiled or treated water)
  - treat symptoms: antidiarrheal agents (e.g. bismuth salicylate, loperamide)
  - empiric antibiotics in moderate or severe illness: ciprofloxacin or azithromycin or rifaximin
- note: there is increasing fluoroquinolone resistance in causative agents, especially in Southeast Asia

**Prevention**
- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
  - bismuth salicylate (Pepto-Bismol®): 60% effective (2 tablets qid according to CDC website)
- CDC Guidelines: antibiotic prophylaxis not recommended
  - increased risk of infection with resistant organisms
- high risk groups (e.g. immunocompromised) likely to be infected with pathogen not covered by standard antimicrobial agents
- Dukoral®: oral vaccine that offers protection against *V. cholerae* (efficacy ~80%) and ETEC (efficacy ~50-67%); the CDC does not recommend it for routine use in travelers

### Chronic Diarrhea

- see [*Gastroenterology*, G16]

### Peptic Ulcer Disease (*H. pylori*)

- see [*Gastroenterology*, G12]

### Bone and Joint Infections

#### Septic Arthritis

**Routes of Infection**
- hematogenous (adults)
- contiguous osteomyelitis (children)
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

**Etiology**
- gonococcal
  - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* species (Group A and B)
  - Gram-negatives: affects neonates, elderly, IV drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae*: affects children aged <2 yr since Hib immunization (Hib possible cause in unvaccinated children)
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* species: prosthetic joints
  - if culture negative: *Borrelia* spp. (*Lyme disease*) or *Tropheryma whippelii* (Whipple's disease)

**Risk Factors**
- gonococcal
  - age (<40 yr), multiple partners, unprotected intercourse, MSM
- non-gonococcal
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (rheumatoid arthritis, osteoarthritis)
  - immunocompromise (DM, chronic kidney disease, alcoholism, cirrhosis)
  - loss of skin integrity (cutaneous ulcer, skin infection)
  - age >80 yr

**Clinical Features of Gonococcal Arthritis**
- two forms (although overlap often)
  - bacteremic form
    - systemic symptoms: fever, malaise, chills
    - gonococcal triad: migratory polyarthralgias, tenosynovitis, dermatitis (pustular skin lesions)
  - septic arthritis form
    - local symptoms in involved joint: swelling, warmth, pain, inability to bear weight, marked decreased in range of motion (see [*Rheumatology*, RH3 for differential diagnosis)

**Clinical Features of Non-Gonococcal Arthritis**
- acute onset of pain, swelling, warmth, decreased range of motion ± fever, chills
- most often in large weight-bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)
Investigations
- consider rheumatologic causes for monoarthritis (see Rheumatology, RH3)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal, and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBCs (>15,000/mm³; likelihood of infection increases with increasing WBCs), PMNs >90%, culture positive
  - growth of *N. gonorrhoeae* from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment

Treatment
- medical
  - empiric IV antibiotics (vancomycin + ceftriaxone) – delay may result in joint destruction
  - Gram stain guides subsequent treatment
  - gonococcal: ceftriaxone + azithromycin, for concurrent treatment of *C. trachomatis*
  - non-gonococcal: antibiotics against *Streptococcus* spp. (2 wk IV f/b PO), *S. aureus* (4 wk IV minimum), or GNB (4 wk)
- surgical drainage if: (see Orthopedics, OR10)
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement
  - prosthetic joint
- daily joint aspirations until culture sterile; no need to give intra-articular antibiotics
- physiotherapy

Prognosis
- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections

Etiology
- neuropathy, peripheral vascular disease, and hyperglycemia contribute to foot ulcers that heal poorly and are predisposed to infection
- organisms in mild infection: *S. aureus, Streptococcus* spp.
- organisms in moderate/severe infection: polymicrobial with aerobes (*S. aureus, Streptococcus, Enterococcus, GNB*) and anaerobes (*Peptostreptococcus, Bacteroides, Clostridium*)

Clinical Features
- not all ulcers are infected
- consider infection if: probe to bone (see below), ulcer present >30 d, recurrent ulcers, trauma, PVD, prior amputation, loss of protective sensation, renal disease, history of walking barefoot
- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) or the presence of pus
- ± crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone → osteomyelitis
- infection severity:
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint) or erythema >2 cm
  - severe = infection in a patient with systemic toxicity (fevers, tachypnea, leukocytosis, tachycardia, hypotension)

Investigations
- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infection)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages) or MRI if high clinical suspicion
  - if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity

Treatment
- evaluate for early surgical debridement ± revascularization or amputation
- eliminate/reduce pressure and provide regular local wound care
- mild: cephalixin or clindamycin
- moderate: clindamycin + ciprofloxacin or moxifloxacin PO, ceftriaxone or ertapenem IV ± MRSA coverage
- severe: piperacillin/tazobactam or meropenem IV ± vancomycin if MRSA known or suspected
- encourage glycemic control

Does This Patient with Diabetes Have Osteomyelitis of the Lower Extremity? JAMA 2008;299:806-813
Study: Systematic literature review, 21 studies.
Population: 1,027 adult patients with DM being investigated for osteomyelitis.
Intervention: Various aspects of history, physical exam, laboratory tests, and diagnostic imaging studies vs. bone biopsy.
Primary Outcome: Diagnostic utility.
Results: No studies examined any part of history taking. Temperature, ulcer characteristics (erythema, swelling, purulence), elevated WBC, skin swabs, and soft tissue cultures were not useful. Nuclear imaging has poor specificity for osteomyelitis (62-88.5%), and MRIs have greater accuracy in detecting osteomyelitis.

<table>
<thead>
<tr>
<th>Finding</th>
<th>(+) LR</th>
<th>(-) LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visualization of bone</td>
<td>9.2</td>
<td>0.70</td>
</tr>
<tr>
<td>Ulcer area &gt;2 cm²</td>
<td>7.2</td>
<td>0.48</td>
</tr>
<tr>
<td>Probe-to-bone</td>
<td>6.4</td>
<td>0.39</td>
</tr>
<tr>
<td>Clinical judgment</td>
<td>5.5</td>
<td>0.54</td>
</tr>
<tr>
<td>ESR &gt;70 mm/h</td>
<td>11</td>
<td>NS*</td>
</tr>
<tr>
<td>Plain radiographs</td>
<td>2.3</td>
<td>0.63</td>
</tr>
<tr>
<td>MRI</td>
<td>3.8</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*NS = not significant
### Osteomyelitis

- see Orthopedics, OR10

### Cardiac Infections

#### Infective Endocarditis

**Definition**
- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right-sided vs. left-sided
- leaflet vegetations that are comprised of platelet-fibrin thrombi, WBCs, and bacteria

**Risk Factors and Etiology**

- predisposing conditions
  - **high risk:** prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 mo, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - **moderate risk:** other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - **low/no risk:** secundum ASD or surgically repaired ASD < VSD, PDA, MV prolapse, ischemic heart disease, previous CABG
- opportunity for bacteremia: IVDU, indwelling venous catheter, hemodialysis, poor dentition, DM, HIV

**Frequency of valve involvement**

- MV >> AV > TV > PV
  - but in 50% of IVDU-related IE the tricuspid valve is involved

**Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors**

<table>
<thead>
<tr>
<th>Native Valve</th>
<th>IVDU</th>
<th>Prosthetic Valve (recent surgery &lt;2 mo)</th>
<th>Prosthetic Valve (remote surgery &gt;2 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus (36%)</td>
<td>S. aureus (68%)</td>
<td>S. aureus (36%)</td>
<td>Streptococcus (20%)</td>
</tr>
<tr>
<td>S. pneumoniae (28%)</td>
<td>Streptococcus (13%)</td>
<td>S. epidermidis (17%)</td>
<td>S. aureus (20%)</td>
</tr>
<tr>
<td>Enterococcus (11%)</td>
<td>Enterococcus</td>
<td>Other</td>
<td>S. epidermidis (20%)</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>GNB</td>
<td>Enterococcus</td>
<td>Enterococcus (13%)</td>
</tr>
<tr>
<td>GNB</td>
<td>Candida</td>
<td>GNB</td>
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</tr>
<tr>
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</table>

Organisms in bold are the most common isolates.
1. Streptococcus includes mainly Viridans group streptococci
2. Other includes less common organisms such as:
   - Streptococcus (usually associated with underlying GI malignancy, cirrhosis)
   - Culture-negative organisms including nutritionally-deficient streptococci: HACEK, Bartonella, C. burnetii, C. hominis, T. whipplei, Candida
   - Mycobacteria
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = Pseudomonas, saliva = oral flora, toilet water = GI flora)

**Clinical Features**

- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia
- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute MR, AR)
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), headache (mycotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal embolus) ± active sediment
- immune complex
  - Osler’s nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth’s spots (retinal hemorrhage with pale center)

**Diagnosis**

- Modified Duke Criteria, see Table 17
  - definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  - possible diagnosis if: 1 major + 1 minor, OR 3 minor

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**, **

**Osteomyelitis**

- see Orthopedics, OR10

**Cardiac Infections**

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  - glomerulonephritis
  - arthritis
  - Roth’s spots (retinal hemorrhage with pale center)

**Diagnosis**

- Modified Duke Criteria, see Table 17
  - definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  - possible diagnosis if: 1 major + 1 minor, OR 3 minor
Table 17. Modified Duke Criteria

Major Criteria (2)

1. Positive blood cultures for IE
   • Typical microorganisms for IE from 2 separate blood cultures (Streptococcus viridans, HACEK group (see ID17), Streptococcus bovis, Staphylococcus aureus, community-acquired enterococci) OR
   • Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart or all of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1 h apart OR
   • Single positive blood culture for Coxiella burnetii or antiphase I IgG antibody titer >1:800

2. Evidence of endocardial involvement
   • Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve) OR
   • New valvular regurgitation (insufficient if increase or change in preexisting murmur)

Minor Criteria (5)

1. Predisposing condition (abnormal heart valve, IVDU)
2. Fever (100.4°F/38.0°C)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler’s nodes, Roth’s spots
5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE

Investigations

• serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  ▪ persistent bacteremia is the hallmark of endovascular infection (such as IE)
• repeat blood cultures (at least 2 sets) after 48 to 72 h of appropriate antibiotics to confirm clearance
• blood work: CBC and differential (normochromic, normocytic anemia), ESR (increased), RF (+), BUN/Cr
• urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
• ECG: prolonged PR interval may indicate perivalvular abscess
• Echo findings: vegetations, regurgitation, abscess
  ▪ TTE (poor sensitivity) inadequate in 20% (obesity, COPD, chest wall deformities)
  ▪ TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

Treatment

• medical
  ▪ usually non-urgent and can wait for confirmation of etiology before initiating treatment
  ▪ empiric antibiotic therapy if patient is unstable; administer ONLY after blood cultures have been taken
    • first-line empiric treatment for native valve: vancomycin
    • first line empiric treatment for prosthetic valve: vancomycin + gentamicin + cefepime OR a carbapenem
  ▪ targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism, and sensitivities
  ▪ monitor for complications of IE (e.g. CHF, conduction block, new emboli) and complications of antibiotics (e.g. interstitial nephritis)
  ▪ prophylaxis only for high risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure, or musculoskeletal tissue
    • dental/respiratory: amoxicillin single dose 30-60 min prior; clindamycin if penicillin-allergic
    • skin/soft tissue: cephalexin single dose 30-60 min prior; clindamycin if penicillin-allergic (modify based on etiology of skin/soft tissue infection)
• surgical
  ▪ most common indication is refractory CHF
  ▪ other indications include: valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, staphylococci on a prosthetic valve

Prognosis

• adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess, embolization, persistent bacteremia, altered mental status prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess
• mortality: prosthetic valve IE (25-50%), non-IVDU S. aureus IE (30-45%), IVDU S. aureus or streptococcal IE (10-15%)
Neurological Infections

Meningitis

- see Pediatrics, P61

Definition
- inflammation of the meninges

Etiology

Table 18. Common Organisms in Meningitis

<table>
<thead>
<tr>
<th></th>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0-4 wk</td>
<td>GBS</td>
<td>S. pneumonia</td>
<td>HSV-1, 2</td>
<td>Cryptococcus</td>
</tr>
<tr>
<td></td>
<td>E. coli</td>
<td>E. coli</td>
<td>VZV</td>
<td>Coccioides</td>
</tr>
<tr>
<td></td>
<td>L. monocytogenes</td>
<td>S. pneumonia</td>
<td>Enteroviruses</td>
<td>Lyme disease</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>N. meningitidis</td>
<td>L. monocytogenes</td>
<td>West Nile</td>
<td>Neurospilus</td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td>(age &gt; 50 and</td>
<td></td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>comorbidities)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors
- lack of immunization against S. pneumoniae, H. influenzae type b in children
- hematogenous spread after invasion from a mucosal surface (nasopharynx)
- parameningeal focus (otitis media, infection, sinusitis)
- penetrating head trauma
- anatomical meningeal defects – CSF leaks
- previous neurological procedures, shunts
- immunocompromise (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
- contact with colonized or infected persons

Clinical Features
- neonates and children: fever, vomiting, lethargy, irritability, poor feeding
- older children and adults: fever, H/A, neck stiffness, confusion, N/V, lethargy, photophobia, altered level of consciousness, seizures, focal neurological signs, papilledema
- petechial rash in meningococcal meningitis, seen more frequently on trunk or lower extremities

Investigations
- blood work: CBC and differential, electrolytes (for SIADH), blood C&S
  - CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
  - AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
  - PCR for HSV, VZV, enteroviruses, WNV if viral cause suspected
- imaging/neurologic studies: CT, MRI, EEG if focal neurological signs present

Table 19. Typical CSF Profiles for Meningitis

<table>
<thead>
<tr>
<th>CSF Analysis</th>
<th>Bacterial</th>
<th>Viral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
<tr>
<td>Protein (mg/mL)</td>
<td>Markedly Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>WBC</td>
<td>500-10,000/µL</td>
<td>10-500/µL</td>
</tr>
<tr>
<td>Predominant WBC</td>
<td>Neutrophils</td>
<td>Lymphocytes</td>
</tr>
</tbody>
</table>

Treatment
- bacterial meningitis is a medical emergency: do not delay antibiotics for CT or LP
- empiric antibiotic therapy
  - age <1 mo: ampicillin + cefotaxime IV OR ampicillin ± an aminoglycoside IV
  - age >1 mo: vancomycin + cefotaxime OR ceftriaxone IV
  - add ampicillin IV if risk factors for infection with L. monocytogenes present: age >50, alcoholism, immunocompromised
- steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics
  - continue in those patients with proven pneumococcal meningitis
  - not recommended for patients with suspected bacterial meningitis in some resource-limited countries
**Prevention**
- see Pediatrics, P3
- immunization
  - children: immunization against *H. influenzae* (Pentacel®), *S. pneumoniae* (Synflorix®, Prevnar-13®), *N. meningitidis* (Menjugate®, Menactra®)
  - adults: immunization against *N. meningitidis* in selected circumstances (outbreaks, travel, epidemics) and *S. pneumoniae* (Pneumovax®) for high-risk groups
- prophylaxis: close contacts of patients infected with *H. influenzae* should be treated with rifampin if they live with an inadequately immunized (<4 yr) or immunocompromised child (<18 yr); ciprofloxacin, rifampin, or ceftriaxone if close or household contact of a patient with *N. meningitidis*

**Prognosis**
- complications
  - H/A, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness, death
- mortality
  - *S. pneumoniae* 25%; *N. meningitidis* 5-10%; *H. influenzae* 5%
  - worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

**Encephalitis**

**Definition**
- inflammation of the brain parenchyma

**Etiology**
- identified in only 40-70% of cases
  - when cause is identified, the most common etiology is viral
  - e.g. HSV, VZV, EBV, enteroviruses, CMV, West Nile, HIV, mumps, measles, rabies, polio
  - bacteria: *L. monocytogenes*, *Mycobacteria*, spirochetes (Lyme, syphilis)
  - parasites: protozoa (e.g. *Toxoplasma*) and helminths (rare)
  - fungi: e.g. *Cryptococcus*
  - post-infectious (e.g. acute disseminated encephalomyelitis [ADEM])

**Pathophysiology**
- acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response
- viruses may reach the CNS via peripheral nerves (e.g. rabies, HSV)
- herpes simplex encephalitis
  - acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
  - associated with HSV-1, but can also be caused by HSV-2

**Clinical Features**
- constitutional: fever, chills, malaise, N/V
- meningeal involvement (meningoencephalitis): H/A, nuchal rigidity
- parenchymal involvement: seizures, altered mental status, focal neurological signs
- herpes simplex encephalitis
  - acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  - temporal lobe involvement: behavioral disturbance
  - usually rapidly progressive over several days and may result in coma or death
- common sequelae: memory and behavior disturbances

**Investigations**
- CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses, and other less common viral etiologies
- serology: may aid diagnosis of certain causes of encephalitis (e.g. West Nile virus)
- imaging/neurologic studies: CT, MRI, EEG to define anatomical sites affected
- invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
- findings in herpes simplex encephalitis (must rule out due to high mortality)
  - CT/MRI: medial temporal lobe necrosis
  - EEG: early focal slowing, periodic discharges

**Treatment**
- general supportive care
- monitor vital signs carefully
- IV acyclovir empirically until HSV encephalitis ruled out

**Meningococcal Quadrivalent Vaccine**
- *Menactra®* or *Menomune®*
  - Healthy young adults (not immunized in childhood)
  - Asplenia
  - Travelers to high-risk areas
  - Military recruits or laboratory personnel
  - Complement, factor D, or properdin deficiency or acquired terminal complement deficiency through receipt of eculizumab

**Meningitis and encephalitis patients**
- can be distinguished based on their cerebral function. Cerebral function is abnormal in encephalitis patients (e.g. altered mental status, motor or sensory deficits, altered behavior, speech or movement disorders), but may be normal in patients with meningitis. Note however, that there is considerable overlap between the two syndromes ("meningoencephalitis")
Generalized Tetanus

- see Family Medicine, FM3
- see Pediatrics, P3

Etiology and Pathophysiology
- caused by *Clostridium tetani*: motile, spore forming, anaerobic GP bacillus
- found in soil, splinters, rusty nails, GI tract (humans and animals)
- traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wound, burns, nonsterile surgeries or deliveries)
- upon inoculation, spores transform into *C. tetani* bacilli that produce tetanus toxin
  - toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  - net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

Clinical Features
- generalized tetanus
  - initially present with painful spasms of masseters (trismus or “lockjaw”)
  - sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  - paralysis descends to involve large muscle groups (neck, abdomen)
  - apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
- autonomic hyperactivity
  - diaphoresis, tachycardia, HTN, fever as illness progresses

Investigations
- primarily a clinical diagnosis, often although not always with a history of a traumatic wound and lack of immunization
- culture wounds, CK may be elevated

Treatment
- stop toxin production
  - wound debridement to clear necrotic tissue and spores
  - antimicrobial therapy: IV metronidazole, penicillin G IV is an effective alternative
- neutralize unbound toxin with tetanus immune globulin (TIG)
- supportive therapy: intubation, spasmyloytic medications (benzodiazepines), quiet environment, cooling blanket
- control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate

Prevention
- infection with *C. tetani* does not produce immunity – vaccinate patients on diagnosis
- tetanus toxoid vaccination (see Pediatrics, P3/Emergency Medicine, ER17)

Rabies

Definition
- acute progressive encephalitis caused by RNA virus (family: Rhabdoviridae, genus Lyssavirus)

Etiology and Pathophysiology
- any mammal can transmit the rabies virus
  - most commonly transmitted by raccoon, skunk, bat, fox, cat, and dog; monkeys also a risk in the developing world
- transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
- almost all cases due to bites
- virus travels via retrograde axonal transport from PNS to CNS
- virus multiples rapidly in brain, then spreads to other organs, including salivary glands
- development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
- infected animal can transmit rabies virus as soon as it shows signs of disease

Clinical Features
- five stages of disease
  1. incubation period
  2. prodrome (<1 wk)
  3. influenza-like illness: low-grade fever, malaise, anorexia, N/V, H/A, sore throat
  4. pain, pruritus, paresthesia may occur at wound site
once prodromal symptoms develop, there is rapid, irreversible progression to death

progression from prodrome to coma and death may occur without an intervening acute neurologic syndrome

3. acute neurologic syndrome: 3 types (<1 wk)
   a. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia, hypersalivation, fever, seizures
      • painful pharyngeal spasms on encountering gust of air or swallowing water cause aerophobia and hydrophobia, respectively
   b. paralytic: quadriplegia, loss of anal sphincter tone, fever
c. atypical: rare

4. coma
   ▪ complete flaccid paralysis, respiratory and cardiovascular failure
5. death (within days to weeks of initial symptoms)

Investigations

• purpose of diagnosis by investigations is to limit patient contact with others and to identify others exposed to the infectious source
• ante-mortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy, serum, CSF
• post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion bodies in neurons)

Treatment

• post-exposure prophylaxis depends on regional prevalence (contact Public Health) and circumstances surrounding injury
• three general principles
  ▪ wound care: clean wound promptly and thoroughly with soap and running water
  ▪ passive immunization: HRIg infiltrated into wound site, with any remaining volume administered IM in anatomical site distant from vaccine administration
  ▪ active immunization: inactivated rabies virus vaccine (series of shots post-exposure)
• treatment is supportive once victim manifests signs and symptoms of disease

Prevention

• pre-exposure vaccination
  ▪ recommended for high risk persons: laboratory staff working with rabies, veterinarians, animal and wildlife control workers, long-term travelers to endemic areas

Systemic Infections

Sepsis and Septic Shock

• see Respirology, R33

Definitions

• systemic inflammatory response syndrome (SIRS): two or more of
  1. temperature <96.8°F/36°C or >100.4°F/38°C
  2. heart rate >90 beats per minute
  3. respiratory rate >20 breaths per minute or PaCO2 <32 mmHg
  4. WBC <4 x 10^9/L or >12 x 10^9/L or >10% bands
• sepsis: SIRS + proven or provable infection
• severe sepsis: sepsis + signs of end-organ dysfunction and hypoperfusion
• septic shock: severe sepsis + hypotension (<90 mmHg sBP), despite adequate fluid resuscitation

Pathophysiology

• causative agents are identified in only 50-70% of cases
• when organisms are identified, GP and GN organisms are the cause in 90% of cases
• primary bloodstream infection or secondary bacteremia → local immune response → immune cells release pro-inflammatory cytokines → immune response spreads beyond local environment → unregulated, exaggerated systemic immune response → vasodilation and hypotension → involvement of tissues remote from the site of injury/infection resulting in multiple major organ dysfunction → periodic immunoparalysis

Clinical Features

• history: fever, chills, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
• physical: abnormal vitals (fever, tachypnea, tachycardia, hypotension), local signs of infection

Investigations

• CBC and differential, electrolytes, BUN, creatinine, liver enzymes, ABG, lactate, INR, PTT, FDP, blood C&S x3, urinalysis, urine C&S and cultures of any wounds or lines
• CXR (other imaging depends on suspicion of focus of infection)
Treatment (also see Respirology, R33)
- respiratory support: O₂ ± intubation
- cardiovascular support: IV fluids, ± norepinephrine + ICU
- IV antibiotics (empirical, depends on suspected source)
  - start with broad spectrum antibiotics (piperacillin/tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology of infection, and local microbial susceptibilities (± aminoglycoside for drug-resistant GNs or vancomycin for MRSA)
  - narrow once susceptibilities are known
- hydrocortisone IV in patients with septic shock unresponsive to fluid resuscitation and vasopressors

Leprosy (Hansen’s Disease)

Etiology
- *Mycobacterium leprae*: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

Clinical Features
- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  i. paucibacillary “tuberculoid” leprosy (intact cell-mediated immune response)
    - ≤5 hypopigmented, well-defined, dry lesions
    - early nerve involvement, enlarged peripheral nerves, neuropathic pain
    - may be self-limited, stable, or progress over time to multibacillary “lepromatous” form
  ii. multibacillary “lepromatous” leprosy (weak cell-mediated immune response)
    - ≥6 lesions, symmetrical distribution
    - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
    - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  iii. borderline leprosy
    - lesions and progression lies between tuberculoid and lepromatous forms

Investigations
- skin biopsy down to fat or slit skin smears for AFB, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

Treatment (WHO Treatment Regimens)
- paucibacillary: dapsone + rifampin monthly x 6 mo
- single skin lesion paucibacillary: single dose of rifampicin, ofloxacin, and minocycline
- multibacillary and borderline: dapsone + rifampin monthly + clofazimine monthly x 12 mo
  - AND low dose clofazimide once daily x 12 mo
- treatment of leprosy can cause an immune reaction to killed bacteria (e.g. erythema nodosum lepromatous or reversal reaction): symptomatic management with NSAIDs if mild, prednisone with 6-12 wk taper if severe; thalidomide for erythema nodosum lepromatous

Prognosis
- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum lepromatous
- long post-treatment follow-up warranted to monitor for relapse and immune reactions

Lyme Disease

Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (N. America), *B. garinii, B. afzelii* (Europe and Asia)
- transmitted by Ixodes tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- small rodents (mice) serve as primary reservoir, while larger animals (white tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment
Clinical Features
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, H/A, myalgias
  - erythema migrans: expanding, non-pruritic bulls-eye (target) lesions (red with clear center) on thigh/groin/axilla
- stage 2 (early disseminated stage): weeks post-infection
  - CNS: aseptic meningitis, CN palsies (CN VII palsy), peripheral neuritis
  - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronicum atrophicans (due to *B. afzelii*)
  - neurologic: encephalopathy, meningitis, neuropathy

Investigations
- serology: ELISA, Western blot

Prevention
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks and prompt removal of tick
- doxycycline prophylaxis within 72 h of removal of an engorged, *Ixodes scapularis* tick in hyperendemic area (local rate of infection of ticks ≥20%) for patients >8 yr who are not pregnant or lactating

Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone

Toxic Shock Syndrome

Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF)
- course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- Staphylococcal TSS involves the production of superantigen TSST-1 (toxic shock syndrome toxin 1)
- Streptococcal TSS involves the production of superantigens SPEA, SPEB, SPEC

Risk Factors
- Staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or Cesarean or other surgical infections)
- Streptococcal: minor trauma, surgical procedures, preceding viral illness (chickenpox), use of NSAIDs

Clinical Features and Investigations
- acute onset
- Staphylococcal TSS
  - T >102°F
  - sBP <90 mmHg
  - diffuse erythroderma with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
- Streptococcal TSS
  - sBP <90 mmHg
  - isolation of GAS from a normally sterile site (e.g. blood, pleural, tissue biopsy, or surgical wound)
  - ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment, erythematous macular rash that may desquamate

Treatment
- supportive: fluid resuscitation
- Staphylococcal: IV clindamycin + (cloxacillin or vancomycin depending on susceptibilities)
- Streptococcal: IV penicillin and clindamycin and IVIg
### Cat Scratch Disease

**Etiology**
- *Bartonella henselae*: intracellular bacteria
- cat-to-human transmission via cat scratch/bite

**Clinical Features**
- skin lesion appears 3-10 d post-inoculation
- may be followed by fever, tender regional lymphadenopathy
- in some patients, organism may disseminate causing hepatosplenomegaly, neurologic symptoms
- usually self-limited

**Investigations**
- serology, lymph node biopsy

**Treatment**
- supportive in most cases
- azithromycin x 10-14 d in patients with moderate-severe disease or immunocompromise

### Rocky Mountain Spotted Fever

**Etiology**
- *Rickettsia rickettsii*: obligate intracellular GN organism
- reservoir hosts: rodents, dogs
- vectors: *Dermacentor* ticks
- organisms cause inflammation of endothelial lining of small blood vessels, causing small hemorrhages and thrombi
- can cause widespread vasculitis leading to H/A, CNS changes and can progress to death if treatment is delayed

**Clinical Features**
- usually occurs in summer following tick bite
- influenza-like prodrome: acute onset fever, H/A, myalgia, N/V, anorexia
- macular rash appearing on day 2-4 of fever
  - begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  - occasionally “spotless” (10% of patients)

**Investigations**
- skin biopsy and serology (indirect fluorescent antibody test)

**Treatment**
- doxycycline, usually 5-7 d (3 days after afebrile)

### West Nile Virus

**Epidemiology**
- virus has been detected throughout the United States and much of southern Canada
- overall case-fatality rates in severe cases are ~10%

**Transmission**
- primarily from mosquitoes that have fed on infected birds (crows, blue jays)
- transplacental, blood products (rare), organ transplantation

**Clinical Features**
- most are asymptomatic
- most symptomatic cases are mild (West Nile fever): acute onset of H/A, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis and acute flaccid paralysis (especially in those >60 yr)

**Investigations**
- IgM antibody in serum or CSF (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- viral isolation by PCR from CSF, tissue, blood and fluids (all have low sensitivity)
- CSF: elevated lymphocytes and protein if CNS involvement
**Treatment and Prevention**

- Treatment: supportive
- Prevention: mosquito repellent (DEET), drain stagnant water, community mosquito control programs

**Syphilis**

**Etiology**
- *Treponema pallidum*: thick motile spirochetes historically detectable by dark-field microscopy
- Transmitted sexually, vertically, or parenterally (rare)

**Clinical Features**
- See Dermatology, D30 and Gynecology, GY27
- Multi-stage disease
  - Primary syphilis (3-90 d post-infection)
    - Painless chancre at inoculation site (any mucosal surface)
    - Regional lymphadenopathy
    - Acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment
  - Secondary syphilis = systemic infection (2-8 wk following chancre)
    - Maculo-papular non-pruritic rash including palms and soles
    - Generalized lymphadenopathy, low grade fever, malaise, H/A, aseptic meningitis, ocular/otic syphilis
    - Condylomata lata: painless, wart-like lesion on palate, vulva, or scrotum (highly infectious)
  - Latent syphilis
    - Asymptomatic infection that follows untreated primary/secondary syphilis
    - Early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
    - Increased transmission risk with early latent; longer treatment duration required for late latent
  - Tertiary syphilis (1-30 yr post-infection)
    - Gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
    - Aortic aneurysm and aortic insufficiency
    - Neurosyphilis: dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis
  - Congenital syphilis
    - Causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
    - Infants may be asymptomatic until age 2-5 yr then present with rhinitis, lymphadenopathy, hepatosplenomegaly, bone and cartilage degeneration (including saddle nose, saber shins), CN VIII deafness

**Investigations**
- Screening tests: VDRL or RPR (non-treponemal), EIA (treponemal)
- Confirmatory tests: FTA-ABS, MHA-TP, TPPA, TPI, dark field microscopy with silver stain (rarely)
- LP for neurosyphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms, or with HIV and late latent/unknown duration syphilis; consider in others

**Treatment**
- For 1st, 2nd, early latent: benzathine penicillin G 2.4 million units IM x 1
- For 3rd, late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- If allergic to penicillin: doxycycline 100 mg PO bid x 14 d
- Neurosyphilis: aqueous Penicillin G 18-24 million units/d IV x 14 d
- See Family Medicine, FM4S for generalized STD workup
Tuberculosis

Etiology, Epidemiology, and Natural History

• 1/3 of the world’s population is infected with TB
• contracted by aerosolized inhalation of Mycobacterium tuberculosis, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive, and replicate in macrophages
• inhalation and deposition in the lung can lead to one of the following outcomes:
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 95% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 2-3 yr of initial infection) at a pulmonary or extra-pulmonary site

Figure 8. Tuberculosis statistics

Canadian Tuberculosis Standards, 7th ed.

Risk Factors

• social and environmental factors
  ▪ travel or birth in country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  ▪ Aboriginal, crowded living conditions, low SES/homeless, IVDU
  ▪ personal or occupational contact
• host factors
  ▪ immunocompromised/immunosuppressed (especially HIV, including extremes of age)
  ▪ silicosis
  ▪ chronic renal failure requiring dialysis
  ▪ malignancy and chemotherapy
  ▪ substance abuse (e.g. drug use, alcoholism, smoking)

Clinical Features

• primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
• secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms
  i. pulmonary TB
    ▪ chronic productive cough ± hemoptysis
    ▪ CXR consolidation or cavitation, lymphadenopathy
    ▪ non-resolving pneumonia despite standard antimicrobial therapy
  ii. miliary TB
    ▪ widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
    ▪ CXR: multiple small 2-4 mm millet seed-like lesions throughout lung
  iii. extrapulmonary TB
    ▪ lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott’s disease), adrenal (causing Addison’s disease), renal, ovary

Tuberculosis Polyserositis

Pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)

Incidence rate per 100,000 population

*Population denominations obtained from Statistics Canada
**Investigations**
- screening for latent TB
  - PPD/Mantoux skin tests
    - both tests diagnose prior TB exposure; neither can diagnose or exclude active disease
  - IFN-γ release assay (IGRA):
    - in patients previously infected with TB, T-cells produce increased amounts of IFN-γ when re-exposed to TB antigen
    - detects antigen not present in the BCG vaccine or in most types of non-tuberculous-mycobacteria (NTM), therefore fewer false positives
  - American guidelines treat IGRAs as equivalent to the TB skin test and preferable in patients with a history of BCG vaccination or who may not return for skin test reading
- diagnostic tests/investigations for active pulmonary TB
  - morning sputum on 3 consecutive days for acid-fast bacilli smear and culture
  - BAL
  - CXR
    - nodular or alveolar infiltrates with cavitation (middle/lower lobe if primary, apical if secondary)
    - pleural effusion (usually unilateral and exudative) may occur independently of other radiograph abnormalities
    - hilar/mediastinal adenopathy (especially in children)
    - tuberculoma (semi-calcified well-defined solitary coin lesion 0.5-4 cm that may be mistaken for lung CA)
    - miliary TB
    - evidence of past disease: calcified hilar and mediastinal nodes, calcified pulmonary focus, pleural thickening with calcification, apical scarring

**Prevention**
- primary prevention
  - airborne isolation for active pulmonary disease
  - BCG vaccine
    - ~80% effective against pediatric miliary and meningal TB
    - effectiveness in adults debated (anywhere from 0-80%)
    - routine use rarely recommended in American population, however widely used in other countries
- secondary prevention (defer in pregnancy unless mother is high risk)
  - likely INH-sensitive: isoniazid (INH) + pyridoxine (vit B6 to help prevent INH-associated neuropathy) x 9 mo
  - likely INH-resistant: rifampin x 4 mo

**Treatment of Active Infection**
- empiric therapy: INH + rifampin + pyrazinamide + ethambutol + pyridoxine
- pulmonary TB: INH + rifampin + pyrazinamide + ethambutol + pyridoxine x 2 mo (initiation phase), then INH + rifampin + pyridoxine x 4 mo in fully susceptible TB (continuation phase), total 6 mo
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
  - MDR = resistance to INH and rifampin ± others
  - XDR = resistance to INH + rifampin + fluoroquinolone + ≥1 of injectable, second-line agents
  - very difficult to treat, global public health threat
  - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Center for Disease Control website http://www.cdc.gov/tb/ for more information)
HIV and AIDS

Epidemiology

American Situation (Center for Disease Control, 2012)
- at the end of 2009, an estimated 1,148,200 persons aged 13 and older were living with HIV infection in the United States, including 207,600 (18.1%) persons whose infections had not been diagnosed
- approximately 50,000 people in the United States are newly infected with HIV each year; in 2010 (the most recent year that data are available), there were an estimated 47,500 new HIV infections

Global Situation (WHO and UNAIDS Core Epidemiology Slides, December 2013)
- estimated 35.5 million people living with HIV/AIDS in 2012
- estimated 2.3 million newly infected in 2012
- estimated 1.6 million AIDS-related deaths in 2012

Definition and Pathophysiology

- HIV is a retrovirus that causes progressive immune system dysfunction which predisposes patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17) and capsid (p24) enclosing 2 single-stranded copies of RNA + enzymes in its core
- virion glycoproteins bind CD4 and CXCR4/CCR5 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by reverse transcriptase; dsDNA is integrated into host genome
- virus DNA transcribed and translated using host cell machinery, post-translational modifications include proteolytic activity of virally encoded protease enzymes
- newly produced virions bud out of host cell, incorporating host cell membrane; additional maturation steps are required before virion is considered infectious
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, increased cell turnover

Modes of Transmission

Table 20. Modes of Transmission by Site and Medium

<table>
<thead>
<tr>
<th>HIV Invasion Site</th>
<th>Sub-Location</th>
<th>Transmission Medium</th>
<th>Transmission Probability per Exposure Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital tract</td>
<td>Vagina, ectocervix, endocervix</td>
<td>Semen</td>
<td>1 in 200 to 1 in 2,000</td>
</tr>
<tr>
<td>Male genital tract</td>
<td>Inner foreskin, penile urethra</td>
<td>Cervicovaginal and rectal secretions and desquamations</td>
<td>1 in 700 to 1 in 3,000</td>
</tr>
<tr>
<td>Intestinal tract</td>
<td>Rectum</td>
<td>Semen</td>
<td>1 in 20 to 1 in 300</td>
</tr>
<tr>
<td></td>
<td>Upper GI tract</td>
<td>Semen</td>
<td>1 in 2,500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal blood/genital secretions (intrapartum)</td>
<td>1 in 5 to 1 in 10</td>
</tr>
<tr>
<td>Placenta</td>
<td>Chorionic villi</td>
<td>Maternal blood (intrauterine)</td>
<td>1 in 10 to 1 in 20</td>
</tr>
<tr>
<td>Blood stream</td>
<td></td>
<td>Contaminated blood products</td>
<td>95 in 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sharp/needlestick injuries</td>
<td>1 in 150</td>
</tr>
</tbody>
</table>

Adapted with permission from Macmillan Publishers Ltd. Nat Rev Immunology 2008;8:447-457

NOTE: these estimates are for “all comers” i.e. they estimate transmission risk for anyone with HIV infection and do not take into account treatment status of the HIV+ person (in contrast to results of PARTNER study)
Natural History

Figure 10. Relationships between CD4 T-cell count, viral load, and anti-HIV antibodies

Acute (Infection) Retroviral Syndrome
- 40-90% experience an acute ‘flu-like’ illness (may include fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, H/A, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high risk of transmission

Asymptomatic (Latent) Stage
- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count: 500-1,100 cells/mm³
- CD4 count drops 60-100 cells/mm³ per year
- by 10 yr post-infection, 50% have AIDS, 30% demonstrate milder symptoms, and <20% are asymptomatic if left untreated

AIDS Definition in United States
- CD4+ T-lymphocyte count of <200 cells/μL OR
- CD4+ T-lymphocyte percentage of total lymphocytes of <14% OR
- documentation of an AIDS-defining condition

Table 21. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)

<table>
<thead>
<tr>
<th>CD4 Counts</th>
<th>Possible Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 cells/mm³</td>
<td>Often asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Constitutional symptoms: fever, night sweats, fatigue, weight loss</td>
</tr>
<tr>
<td></td>
<td>Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi’s sarcoma (KS)</td>
</tr>
<tr>
<td></td>
<td>Recurrent bacterial infections, especially pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pulmonary and extrapulmonary tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Lymphoma</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>Pneumocystis jiroveci pneumonia (formerly PCP)</td>
</tr>
<tr>
<td></td>
<td>KS</td>
</tr>
<tr>
<td></td>
<td>Oral thrush</td>
</tr>
<tr>
<td></td>
<td>Local and/or disseminated fungal infections: Cryptococcus neoformans, Coccioidoides immitis, Histoplasma capsulatsum</td>
</tr>
<tr>
<td>&lt;100 cells/mm³</td>
<td>Progressive multifocal leukoencephalopathy (PML) – JC virus</td>
</tr>
<tr>
<td></td>
<td>CNS toxoplasmosis</td>
</tr>
<tr>
<td>&lt;50 cells/mm³</td>
<td>CMV infection: retinitis, colitis, cholangiopathy, CNS disease</td>
</tr>
<tr>
<td></td>
<td>Mycobacterium avium complex (MAC)</td>
</tr>
<tr>
<td></td>
<td>Bacillary angiomatosis (disseminated Bartonella)</td>
</tr>
<tr>
<td></td>
<td>Primary central nervous system lymphoma (PCNS/L)</td>
</tr>
</tbody>
</table>

Laboratory Diagnosis
- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo (therefore 3 mo window period)
- initial screening test (3rd generation antibody test): enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%
• ART leads to 96% reduction in risk of transmitting HIV to sexual partners
• strong evidence against intermittent HAART or 'drug holidays'
• goal: keep viral load below limit of detection i.e. <40 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo and restore immunological function
• ART improves prognosis
• effective in decreasing HIV transmission
• ART and prevention of further transmission through safer sex and clean needles for injection drug use
• ART improves cardiovascular health
• ART decreases risk of transmission; strength of evidence supporting that recommendation changes depending on clinical and psychosocial factors on case by case basis
• ART does not protect against HIV superinfection (transmission of different HIV strains from another HIV+ person) does rarely occur so barrier protection during sex is still recommended
• ART improves prognosis
• ART improves cardiovascular health
• ART decreases risk of transmission; strength of evidence supporting that recommendation changes depending on clinical and psychosocial factors on case by case basis
• ART does not protect against HIV superinfection (transmission of different HIV strains from another HIV+ person) does rarely occur so barrier protection during sex is still recommended

Management of the HIV-Positive Patient

• verify positive HIV test
• complete baseline history and physical exam, then follow-up every 3-6 mo
• laboratory evaluation
  • routine CD4 count to measure status of the immune system
  • routine HIV-RNA levels (viral load)
    • also important indicator of effect of ART
  • baseline HIV resistance testing to guide ARV therapy
  • HLA-B*5701 genetic test to screen for abacavir hypersensitivity
  • baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
  • baseline serologies (hepatitis A, B, and C, syphilis, toxoplasma, CMV, VZV)
  • routine biochemistry and hematology, CXR
  • annual fasting lipid profile and fasting glucose (due to HAART side effects)
• education
  • regular follow-up on CD4 counts and viral loads (q3-6 mo) as well as strict adherence to ART improves prognosis
  • prevention of further transmission through safer sex and clean needles for injection drug use
  • HIV superinfection (transmission of different HIV strains from another HIV+ person) does rarely occur so barrier protection during sex is still recommended
  • discuss importance of disclosing HIV status to partners including risk of criminal prosecution of non-disclosure in jurisdictions where applicable
  • connect to relevant community groups and resources
• health care maintenance
  • assessment of psychosocial concerns and referral to psychiatry or social work if appropriate
  • vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative)
  • annual screening (PAP smear, STDs)
  • management of comorbid conditions and provision of general primary care

Table 22. Prophylaxis Against Opportunistic Infections in HIV-Infected Patients

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication for Prophylaxis</th>
<th>Prophylactic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis jiroveci</td>
<td>CD4 count &lt;200 cells/mm³ or history of oral candidiasis</td>
<td>TMP-SMX 1 SS or DS OD</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>IgG antibody to Toxoplasma and CD4 count &lt;100 cells/mm³</td>
<td>As per prophylaxis for pneumocystsis</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>PPD reaction &gt;5 mm or contact with case of active TB</td>
<td>INH + pyridoxine daily x 9 mo</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>CD4 count &lt;50 cells/mm³</td>
<td>Azithromycin 1,200 mg q1wk</td>
</tr>
</tbody>
</table>

SS = single strength; DS = double strength


Anti-Retroviral Treatment

Overall Treatment Principles
• recommended that all HIV+ patients initiate HAART to prevent disease progression and transmission; strength of evidence supporting that recommendation changes depending on CD4 count and sexual practices (AI evidence that CD4 <350 should be on HAART)
• patients starting HAART should be committed to treatment and understand the importance of adherence; poor compliance can lead to viral resistance; may defer treatment on the basis of CD4 count and sexual practices (AI evidence that CD4 <350 should be on HAART)
• initiate ART if opportunistic infection/malignancy, pregnancy, HIV-associated nephropathy, HIV-associated thrombocytopenia, need for hepatitis B therapy in HBV co-infected patients
• consider starting treatment early if HCV co-infection, high HIV viral load, comorbid conditions (e.g. cardiovascular disease)
• consider results of baseline resistance testing and complete ART history before (re-)initiating HAART
• goal keep viral load below limit of detection i.e. <40 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo and restore immunological function
• strong evidence against intermittent HAART or ‘drug holidays’
• ART leads to 96% reduction in risk of transmitting HIV to sexual partners
HAART Recommendations for Treatment of Naïve Patients

- 2 NRTIs + 1 NNRTI/PI (boosted with ritonavir) / INSTI

Treatment Failure

- defined clinically (HIV progression), immunologically (failure to increase CD4 count by 25-50 over first year of treatment or CD4 decrease >100 over 1 yr), or virologically (failure to achieve viral load <40 copies/mL after 6 mo)
- ensure that viral load >40 is not just a transient viremia or 'blip'; confirm medication adherence, assess drug interactions, resistance testing

Table 23. Anti-Retroviral Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors (NRTIs)</td>
<td>zidovudine (AZT)</td>
<td>Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth</td>
<td>Lactic acidosis, Lipodystrophy, Rash, N/V/diarrhea, Bone marrow suppression (AZT), Peripheral neuropathy (ddI, d4T), Drug-induced hypersensitivity (ABC), Pancreatitis (ddI/d4T), Myopathy (AZT)</td>
</tr>
<tr>
<td>Combination Tablets:</td>
<td>zidovudine (AZT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>lamivudine (3TC)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>stavudine (d4T)</td>
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<td></td>
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<tr>
<td></td>
<td>didanosine (ddI)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>abacavir (ABC)</td>
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<td></td>
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<tr>
<td></td>
<td>emtricitabine (FTC)</td>
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<td></td>
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<tr>
<td></td>
<td>tenofovir disoproxil fumarate (TDF)</td>
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</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</td>
<td>efavirenz (EFZ)</td>
<td>Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication</td>
<td>Rash, Stevens-Johnson syndrome, CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz), Hepatotoxicity (nevirapine – avoid in females with CD4 &gt;250, men with CD4 &gt;400), CYP3A4 interactions</td>
</tr>
<tr>
<td></td>
<td>nevirapine (NVP)</td>
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<tr>
<td></td>
<td>delavirdine (DLV)</td>
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<td></td>
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<tr>
<td></td>
<td>etravirine (ETR)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>ribavirine (Rpv)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PIs)*</td>
<td>ritonavir (RTV)</td>
<td>Prevent maturation of infectious virions by inhibiting the cleavage of polyproteins</td>
<td>Lipodystrophy, metabolic syndrome, N/V/diarrhea, Nephrolithiasis (indinavir, ritonavir), Rash (APV), Hyperbilirubinemia (atazanavir, indinavir), CYP3A4 interactions, Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>saquinavir (SQV)</td>
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<tr>
<td></td>
<td>amprenavir (APV)</td>
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<td></td>
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<tr>
<td></td>
<td>nelfinavir (NFV)</td>
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<td></td>
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<tr>
<td></td>
<td>indinavir (IDV)</td>
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<td></td>
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<td></td>
<td>atazanavir (ATV)</td>
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<td></td>
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<tr>
<td></td>
<td>fosamprenavir (FPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tipranavir/ritonavir (Kaletra®)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>tipranavir (TPV)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>darunavir (DRV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>enfuvirtide (T-20)</td>
<td>Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection</td>
<td>Injection site reactions, rash, infection, diarrhea, nausea, fatigue</td>
</tr>
<tr>
<td>CCR5 antagonist</td>
<td>maraviroc</td>
<td>Inhibit viral entry by blocking host CCR5 co-receptor</td>
<td>Fever, cough, dizziness</td>
</tr>
<tr>
<td>Integrase strand transfer inhibitors (INSTIs)</td>
<td>raltegravir</td>
<td>Inhibits integration of HIV DNA into the human genome thus preventing HIV replication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>elvitegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>doltegravir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations

Single Tablet ART Regimens

- reduces pill burden and increases adherence
- generally better tolerated

Table 24. Single Tablet HAART Regimens

<table>
<thead>
<tr>
<th>Name</th>
<th>Contents</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla®</td>
<td>efavirenz/tenofovir/emtricitabine</td>
<td>psychiatric events, vivid dreams</td>
</tr>
<tr>
<td>Complera®</td>
<td>ritonavir/abacavir/tenofovir</td>
<td>good side effect profile</td>
</tr>
<tr>
<td>Stribild®</td>
<td>abacavir/emtricitabine/tenofovir</td>
<td>good side effect profile</td>
</tr>
</tbody>
</table>
Prevention of HIV Infection

- education, including harm-reduction
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm reduction for injection drug users: avoid sharing needles
- treatment of HIV+ women with HAART during the 2nd and 3rd trimester of pregnancy and AZT during delivery followed by treatment of the infant for 6 wk (decreases maternal-fetal transmission from 25% to <3%)
- universal blood and body precautions for health care workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV although additional data needed
- ART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation
**Types of Testing**

1. **Nominal/Name-Based HIV Testing**
   - the person ordering the test knows the identity of the person being tested for HIV
   - the HIV test is ordered using the name of the person being tested
   - person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
   - the test result is recorded in the health care record of the person being tested

2. **Non-Nominal/Non-Identifying HIV Testing**
   - similar to nominal/name-based testing on all points except:
     - the HIV test is ordered using a code or the initials of the person being tested

3. **Anonymous Testing**
   - available at specialized clinics
   - the person ordering the HIV test does not know the identity of the person being tested
   - the HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
   - test results are not recorded on the health care record of the person being tested
   - patient identification and notification of Public Health required to gain access to ART

**HIV Pre- and Post-Test Counseling**

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counseling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV+ patients should be connected with local support services

**Fungal Infections**

**Skin and Subcutaneous Infections**

**Superficial Fungal Infections**

- see Dermatology, D23

**Dermatophytes**

- see Dermatology, D25

**Subcutaneous Fungal Infection**

**Pathophysiology**

- fungi that naturally reside in soil and enter skin via traumatic break
- *Sporothrix schenckii*: most commonly affects gardeners injured by a rose thorn or splinter
  - causes subcutaneous nodule at point of entry
  - fungi may migrate up lymphatic vessels creating nodules along the way – “nodular lymphangitis”

**Treatment**

- oral azole (e.g. itraconazole)
- IV amphotericin B for severe or disseminated infection

**Endemic Mycoses**

**Basics**

- three major endemic mycoses in North America
  - histoplasmosis
  - blastomycosis
  - coccidioidomycosis
• thermally dimorphic organisms: mold in cold temperature (e.g. soil) and yeast at higher temperature (e.g. tissue)
• infection occurs through inhalation of spores (soil, bird droppings, vegetation) or inoculation injury
• all can cause pneumonia and may disseminate hematogenously
• may reactivate or disseminate during immunocompromise

Treatment
• common to all endemic mycoses
  ▪ oral azole (e.g. itraconazole for mild-moderate local infection)
  ▪ IV amphotericin B for systemic infection

<table>
<thead>
<tr>
<th>Table 25. Endemic Mycoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease</strong></td>
</tr>
<tr>
<td>_________________________</td>
</tr>
<tr>
<td>Histoplasma capsulatum</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
</tr>
</tbody>
</table>

Opportunistic Fungi

**Pneumocystis jiroveci** (formerly P. carinii)

Microbiology
• unicellular fungi
• previously classified as a protozoa

Transmission
• rarely person-to-person transmission
• most disease is due to reactivation of latent infection acquired by the respiratory route or reinfection by a different genotype
• causes clinical disease in immunocompromised patients (steroid use, HIV)
  • 80% lifetime risk without prophylaxis (TMP/SMX) in HIV patients with CD4 count <200 cells/mm³

Clinical Features
• symptoms of pneumonia: fever, nonproductive cough, progressive dyspnea
• classic CXR

Investigations
• demonstration of organism in induced sputum, bronchoalveolar lavage, or endotracheal aspirate (if intubated)
Treatment and Prevention
- oxygen to keep $\text{SaO}_2 > 90\%$
- antimicrobial options
  - TMP/SMX (PO or IV) *First line
  - dapsone and TMP
  - clindamycin and primaquine
  - pentamidine (IV)
  - atovaquone
- corticosteroids used as adjuvant therapy in those with severe hypoxia ($\text{pO}_2 < 70 \text{ mmHg}$ or $\text{A-a} \text{ gradient O}_2 > 35 \text{ mmHg}$)
- prophylactic TMP/SMX for those at high risk of infection (HIV patients when CD4 < 200 cells/mm$^3$ or non-HIV immunocompromised patients under specific conditions)

\textbf{Cryptococcus spp.}

Microbiology
- encapsulated yeast found worldwide
- 2 human pathogenic species: \textit{C. gattii}, \textit{C. neoformans}

Transmission
- inhalation of airborne yeast from soil contaminated with pigeon droppings (\textit{C. neoformans}) or certain tree species such as Eucalyptus or Douglas fir (\textit{C. gattii}) may cause local infection in lung → asymptomatic or pneumonia
- may also spread hematogenously to the CNS, skin, bones, and other organs
- \textit{C. neoformans} tends to affect immunocompromised hosts
- \textit{C. gattii} tends to affect immunocompetent hosts

Clinical Features
- pulmonary
  - usually asymptomatic or self-limited pneumonitis
  - only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
- disseminated
  - frequently disseminates in HIV+ population
  - CNS: meningitis (leading cause of meningitis in patients with HIV)
  - skin: umbilicated papules that resemble large lesions of \textit{Molluscum contagiosum}

Investigations
- serum cryptococcal antigen
- CSF for meningitis: India-ink stain, cryptococcal antigen test, culture to confirm

Treatment
- in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  - amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  - switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance

\textbf{Candida albicans}

Microbiology
- yeast forms with pseudohyphae at 68°F/20°C and germ tube formation at 86°F/37°C

Transmission
- normal flora of skin, mouth, vagina, and GI tract
- risk factors for overgrowth
  - immunocompromised state (DM, corticosteroids)
  - ICU patients (broad-spectrum antibiotic use, central venous catheters, TPN)
  - obesity → maceration and moisture in intertriginous areas, pannus, under breasts

Clinical Features
- mucocutaneous
  - oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY24), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  - small satellite lesions beyond the margin of the rash
- invasive
  - candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease
Treatment
- thrush: nystatin suspension or pastilles for mild disease, fluconazole for severe disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

Aspergillus spp.

Microbiology
- branching septate hyphae
- common species causing disease include *A. fumigatus, A. flavus*

Transmission
- ubiquitous in the air and the environment
- *Aspergillus* produces a toxin called aflatoxin that contaminates nuts, grains, and rice

Clinical Features
- allergic bronchopulmonary aspergillosis (ABPA)
  - IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
  - occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
  - ball of hyphae in a preexisting lung cavity
  - symptoms range from asymptomatic to massive hemoptysis
  - CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes ("air crescent" sign)
- invasive aspergillosis
  - associated with prolonged and persistent neutropenia or transplantation
  - pneumonia – most common
  - may disseminate to other organs: brain, skin
  - severe symptoms with fever, cough, dyspnea, cavitation; fatal if not treated early and aggressively
  - CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules with surrounding ground glass ("halo" sign)
- mycotoxicosis
  - aflatoxin produced by *A. flavus* (nuts, grains, rice)
  - results in liver necrosis and hepatocellular carcinoma

Treatment Options
- for invasive aspergillosis: voriconazole or amphotericin B
- surgical resection for aspergilloma
- corticosteroids ± itraconazole for ABPA

Parasitic Infections

Protozoa – Intestinal/Genitourinal Infections

*Entamoeba histolytica* (Amoebas)

Transmission
- reservoir: infected humans
- cysts by fecal-oral and food/waterborne transmission in areas of poor sanitation
- seen in immigrants, travelers, institutionalized individuals, Aboriginals, MSM

Clinical Features
i. asymptomatic carriers
ii. amoebic dysentery
- abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea
- secondary to local tissue destruction and ulceration of large intestine
iii. amoebic abscesses
- most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
- can also occur in lungs and brain

![Figure 12. Entamoeba life cycle](image-url)
Investigations
- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- *E. histolytica* indistinguishable microscopically from the non-pathogen *E. dispar* (distinguish by specific stool antigen detection)

Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)

---

**Giardia lamblia**

Transmission
- reservoir: infected humans and other mammals
- food/waterborne (especially in the Rockies) and fecal-oral transmission of infectious cysts
- risk factors: travel, camping, institutions, day care centers, MSM

Clinical Features
- giardiasis (“beaver fever”)
- symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats small intestine and thus prevents fat absorption)
- nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
- no hematochezia (no invasion into intestinal wall), no mucus in stool

Investigations
- multiple stool samples (daily x 3 d) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

Treatment and Prevention
- metronidazole, nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

---

**Trichomonas vaginalis**

Transmission
- sexual contact

Clinical Features
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- trichomonas vaginitis (see Gynecology, GY25)
- vaginal discharge (profuse, malodorous, yellow-green or gray, frothy), pruritus, dysuria, dyspareunia

Investigations
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

Treatment
- metronidazole for patient and partner(s)

---

**Cryptosporidium spp.**

Transmission
- reservoir: infected humans and a wide variety of young animals
- fecal-oral transmission by ingestion of cysts, waterborne
- risk factors: summer and fall, young children (day care), MSM, contact with farm animals, immunocompromise, immune reconstitution

Clinical Features
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with N/V, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)
Investigations
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody

Treatment and Prevention
- supportive care
  - in HIV, try HAART to restore immunity; if fails, try nitazoxanide
  - good personal hygiene, water filtration

Blood and Tissue Infections

*Plasmodium* spp. (Malaria)

Microbiology
- species include: *P. falciparum* (most common and most lethal), *P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi* (new species isolated from primates in Malaysia, potentially fatal)
- complex life cycle: human host for asexual reproduction and mosquito for sexual reproduction
- sporozoite from mosquitoes infect liver cells in which parasites multiply and are released as merozoites which infect RBCs causing disease
- *P. ovale* and *P. vivax* can produce dormant hypnozoites in the liver that may cause relapsing malaria due to reactivating (entering the erythrocytic cycle) after many months

Transmission
- reservoir: infected human
- transmission by the night-biting female *Anopheles* mosquito, vertical transmission, and blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

Clinical Features
- flu-like prodrome
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of RBCs) (lasts several hours)
  - *P. falciparum* and *P. ovale*: chills and fever q48h but can be variable
  - *P. malariae*: chills and fever q2-7 days but can be variable
  - *P. falciparum*: less predictable fever interval, can be highly variable (>90% ill within 30 d)
- abdominal pain, diarrhea, myalgia, H/A, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis

Complications
- *P. falciparum*: CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute renal failure, ARDS, primarily responsible for fatal disease
- *P. knowlesi*, and rarely *P. vivax* can be fatal

Investigations
- microscopy: blood smear q12-24h (x3) to rule out infection
  - thin smear (Giemsa stain) for presence of organisms
  - thick smear (Giemsa stain) for species identification and quantification of parasites
- rapid antigen detection tests

Treatment and Prevention
- *P. vivax*, *P. ovale*: chloroquine (and primaquine to eradicate liver forms)
- *P. vivax*, chloroquine resistant: primaquine with quinine and doxycycline or tetracycline or mefloquine
- *P. malariae*, *P. knowlesi*: chloroquine
- *P. falciparum*: most areas of the world show chloroquine resistance – check local resistance patterns
  - artemisinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - atovaquone/proguanil combination (Malarone®)
  - quinine plus doxycycline, tetracycline, or clindamycin
  - mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- prevention with antimalarial prophylaxis, covering exposed skin, bed nets, insect repellent

Trypanosoma cruzi

Transmission
- found in Mexico, South America, and Central America
- transmission by Reduviid insect vector ("Kissing Bug"), which defecates on skin and trypomastigotes in the stool are rubbed into bite site by host

Conclusion: Atovaquone-proguanil or doxycycline as prophylaxis against malaria is best tolerated in terms of adverse effects and mefloquine is associated with adverse neuropsychiatric outcomes.
also transmitted via placental transfer, organ donation, blood transfusion, and ingestion of contaminated food containing Reduviid insects (especially cane juice)

Clinical Features
- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation (“Romana’s sign”; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly, and hepatosplenomegaly
  - intermediate phase: asymptomatic but increasing levels of parasite and antibody in blood; most infected persons remain in this phase
  - chronic: can lead to chronic dilated cardiomyopathy, esophagomegaly, and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

Investigations
- wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

Treatment and Prevention
- acute: nifurtimox or benznidazole
- intermediate: increasing trend to treat as acute infection
- chronic: symptomatic therapy, surgery including heart transplant, or esophagectomy, colectomy, as necessary, may be a benefit to antiparasitic treatment
- insect control, bed nets

Toxoplasma gondii

Transmission
- acquired through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), vertical transmission, organ transplantation, gardening without gloves, or whole blood transfusions

Clinical Features
- congenital
  - result of acute primary infection of mother during pregnancy (TORCH infection – see Obstetrics, OB19)
  - stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult → blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
- acquired
  - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
  - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (H/A and focal neurological signs)
  - lymph node, liver, and spleen enlargement and pneumonitis
  - chorioretinitis

Investigations
- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination
- negative serology in many AIDS patients (false negative due to decreased lymphocyte population)

Treatment and Prevention
- no treatment if: immunocompetent, not pregnant, no severe organ damage
- pregnancy: spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folic acid), avoid undercooked meat and refrain from emptying cat litter boxes
- HIV: pyrimethamine + sulfadiazine (see Prophylaxis, ID29)
- eye disease, meningitis: corticosteroids
- proper hand hygiene, cook meat thoroughly to proper temperature

Figure 14. Life cycle of Toxoplasma gondii
### Helminths

#### Roundworms – Nematodes

<table>
<thead>
<tr>
<th>Nematode</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ascaris lumbricoides</em></td>
<td>Tropics</td>
<td>Human feces, ingestion of contaminated food or water</td>
<td>Abdominal pain and intestinal obstruction from high worm burden.</td>
<td>Mebendazole OR albendazole OR pyrantel pamoate</td>
</tr>
<tr>
<td><em>Trichuris trichiura</em> (whipworm)</td>
<td>Tropics</td>
<td>Ingestion of eggs in soil</td>
<td>Diarrhea (+ mucus, blood), abdominal pain, rectal prolapse, stunted growth</td>
<td>Mebendazole OR albendazole</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>Africa, Latin America</td>
<td>Black fly bite</td>
<td>River blindness (onchocerciasis), dermatitis</td>
<td>Ivermectin + doxycycline</td>
</tr>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Tropics</td>
<td>Mosquito bite</td>
<td>Damage to lymphatics resulting in lymphadenopathy, lymphedema, and elephantiasis</td>
<td>Diethylcarbamazine + doxycycline</td>
</tr>
<tr>
<td><em>Loa Loa</em></td>
<td>Central Africa</td>
<td>Deer fly bite</td>
<td>Subcutaneous migration of worm, hypersensitivity in travelers</td>
<td>Diethylcarbamazine, removal of adult</td>
</tr>
<tr>
<td><em>Enterobius vermicularis</em> (Pinworm)</td>
<td>Worldwide</td>
<td>Human host: fecal/oral self-inoculation and fomite person-to-person transfer</td>
<td>Asymptomatic carriers or severe nocturnal perianal itching (pruritus ani) Occasional vaginitis</td>
<td>Mebendazole, in pregnancy, strict hygiene, bleach, personal care, all family members treated simultaneously</td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em> (Threadworm)</td>
<td>Subtropical, tropical, and temperate (including southern US)</td>
<td>Fecal contamination of soil: transmission via unbroken skin, walking barefoot</td>
<td>One of few worms able to multiply in human host. Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration</td>
<td>Ivermectin, 200 µg/kg/d PO x 2 doses (albendazole 40 mg PO bid x 7 d, less effective)</td>
</tr>
</tbody>
</table>

**Figure 15. Life cycle of Enterobius**

1. Embryonated eggs ingested by humans
2. Larvae hatch in small intestine
3. Females migrate out anus at night

**Figure 16. Life cycle of Strongyloides**

1. Step on stool containing larvae
2. Larvae migrate to lungs via bloodstream
3. Larvae crawl up trachea and down to GI tract (cough/swallow)
4. Adult worms in intestine
5. Eggs produced in bowel
6. Larvae
7. Bowel movement containing larvae
Flatworms

Cestodes/Trematodes

Table 27. Cestodes/Trematodes (Flatworms)

<table>
<thead>
<tr>
<th>CESTODES</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taenia solium</td>
<td>Developing countries</td>
<td>Undercooked pork (larvae), human feces (eggs)</td>
<td>Taeniasis: mild abdominal symptoms</td>
<td>Corticosteroids + albendazole for cysticercosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cysticercosis: mass lesions in CNS, eyes, skin, seizures</td>
<td>Antiepileptics if seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Praziquantel for adult tapeworm in gut (taeniasis)</td>
</tr>
<tr>
<td>Taenia saginata</td>
<td>Developing countries</td>
<td>Undercooked beef (larvae)</td>
<td>Mild GI symptoms</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>Diphyllobothrium latum</td>
<td>Europe, North America, Asia</td>
<td>Raw fish</td>
<td>Vitamin B12 deficiency leading to macrocytic anemia and posterior column deficits</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>Echinococcus granulosus</td>
<td>Rural areas</td>
<td>Dog feces (eggs)</td>
<td>Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture) Risk of anaphylaxis if cystic fluid released during surgical evacuation</td>
<td>Albenzole alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREMATODES</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonorchis sinensis</td>
<td>Japan, Taiwan, China, SE Asia</td>
<td>Raw fish</td>
<td>Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma</td>
<td>Praziquantel</td>
</tr>
<tr>
<td>Schistosoma spp.</td>
<td>Africa, SE Asia, focal in Western Hemisphere</td>
<td>Fresh water exposure</td>
<td>Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, SCC of the bladder)</td>
<td>Praziquantel</td>
</tr>
</tbody>
</table>

Trematodes/Flukes

**Schistosoma spp.**

**Species**
- S. mansoni, S. hematobium, S. japonicum

**Transmission**
- larvae (cercariae), released from snails, penetrate unbroken skin in infested fresh water
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach fresh water to hatch; schistosomes cannot multiply in or pass between humans
  - more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa

**Clinical Features**
- most asymptomatic; symptoms seen in travelers (nonimmune)
- Swimmer’s itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, H/A, weight loss, cough, abdominal pain, chronic diarrhea, eosinophilia

**Complications of Chronic Infection**
- S. mansoni, S. japonicum
  - worms in mesenteric vein, eggs in portal tracts of liver and bowel
  - heavy infections: intestinal polyps, portal and pulmonary HTN, splenomegaly (2° to portal HTN), hepatomegaly
- S. hematobium
  - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
  - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
  - neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
- pulmonary complications: granulomatous pulmonary endarteritis, pulmonary HTN, cor pulmonale; especially in patients with hepatosplenic involvement
Investigations
- serology (high sensitivity and specificity), CBC (eosinophilia, anemia, thrombocytopenia)
- *S. mansoni*, *S. japonicum*: eggs in stool, liver U/S shows fibrosis, rectal biopsy
- *S. hematobium*: bladder biopsy, eggs in urine and occasionally stool, kidney and bladder U/S

Treatment and Prevention
- praziquantel
- add glucocorticoid if acute schistosomiasis or neurologic complications develop
- proper disposal of human fecal waste, molluscicide, avoidance of infested water
- do not swim in Lake Malawi

Ectoparasites
- scabies, lice
- see Dermatology, D26

Travel Medicine

General Travel Precautions
- vector-borne: long-sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings and bed nets, exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (Lake Malawi), fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rainfalls
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveler’s diarrhea (bismuth salicylate)
- standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio)
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveler’s diarrhea (bismuth salicylate)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, yellow fever, rabies, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

Infectious Diseases to Consider
- vector-borne: malaria, dengue fever, Chikungunya fever, yellow fever, *Rickettsia*, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, spotted fever, leishmaniasis
- sexually transmitted: HIV, HBV, syphilis, usual STDs
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis
- airborne: TB
- food/water: HAV, HEV, brucellosis, typhoid, paratyphoid, amebiasis, dysentery, traveler’s diarrhea, cholera, *Campylobacter* spp.
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

Fever in the Returned Traveler

Etiology
- commonly identified causes of fever in returning traveler
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)  
  - bacterial: typhoid from *Salmonella* (2-7%), *Rickettsia* (3%)
  - diverse group of causative pathogens: traveler’s diarrhea (10-20%), RTI (10-15%), UTI/STD (2-3%)
- febrile illness in travelers can be caused by routine infections that are common in non-travelers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes: e.g. DVT, PE

History
- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
• persons visiting friends and family more likely to be exposed to local population and pathogens
  ▪ style of travel: lodgings, camping, adventure traveling
  ▪ local population: sick contacts
  ▪ transportation: use of animals
• exposure history
  ▪ street foods, untreated water: increased risk of traveler’s diarrhea, enteric fever
  ▪ uncooked meat/unpasteurized dairy: increased risk of parasitic infection
  ▪ body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  ▪ increased risk of HBV, HCV, HIV, GC, C. trachomatis, syphilis
  ▪ animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies
• fever pattern
  ▪ incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
    ▪ <21 d: consider malaria, typhoid fever, dengue fever, rickettsioses; exclude HBV, TB
    ▪ >21 d: consider malaria, TB; exclude dengue fever, travelers’ diarrhea, rickettsioses
  ▪ body systems affected: GI, respiratory, CNS, skin

### Investigations
• all travelers with fever should undergo the following tests
  ▪ blood work: CBC and differential, liver enzymes, electrolytes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  ▪ urine: urinalysis, urine C&S
• special tests based on symptoms, exposure history, and geography
  ▪ stool: C&S, O&P
  ▪ CXR
  ▪ dengue serology for IgM

### Table 28. Fever in the Returned Traveler

<table>
<thead>
<tr>
<th>Illness</th>
<th>Geography/Timing</th>
<th>Pathogen</th>
<th>Incubation Period</th>
<th>Clinical Manifestations</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Africa India SE Asia Usually rural, night-biting mosquitoes</td>
<td>Plasmodium falciparum Plasmodium vivax P. malariae P. ovale P. knowlesi</td>
<td>10 d to 40 yr</td>
<td>Fever and flu-like illness, (shaking chills, H/A, muscle aches, and fatigue) N/V and diarrhea Anemia and jaundice</td>
<td>Plasmodium falciparum: (severe) kidney failure, seizures, mental confusion, prostration, coma, death, respiratory failure</td>
<td>Antigen detection PCR (mostly a research tool) Artesunate (for severe disease) + malarone, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine</td>
</tr>
<tr>
<td>Dengue</td>
<td>South East Asia Caribbean Usually urban, day-biting mosquitoes</td>
<td>Dengue viruses</td>
<td>3 d to 2 wk</td>
<td>Sudden onset of fever, H/A, retro-orbital pain, myalgias, and arthralgias Leukopenia Thrombocytopenia Hemorrhagic manifestations (rare in travelers)</td>
<td>Anti-dengue IgM positivity</td>
<td>Symptom relief: Acetaminophen (avoid using NSAIDs because of anticoagulant properties)</td>
</tr>
<tr>
<td>Typhoid (enteric fever)</td>
<td>Global but mostly Indian subcontinent</td>
<td>Salmonella typhi/ Salmonella paratyphi</td>
<td>3 to 60 d</td>
<td>Sustained fever 103°-104°F (39°-40°C) Abdominal pain, H/A, loss of appetite, cough, constipation</td>
<td>Stool, urine, or blood sample positive for S. typhi or S. paratyphi</td>
<td>Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone, or macrolide</td>
</tr>
<tr>
<td>Tick Typhus</td>
<td>Mediterranean South Africa India</td>
<td>Rickettsia</td>
<td>1 to 2 wk</td>
<td>Fever, H/A, fatigue, muscle aches, occasionally rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes</td>
<td>Serology Presence of classic tick eschar</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>TB</td>
<td>Global</td>
<td>M. tuberculosis Variable</td>
<td>Variable</td>
<td>Fever, cough, hemoptysis</td>
<td>CXR Sputum culture and acid-fast stain</td>
<td>Ethambutol, isoniazid, pyrazinamide, rifampin</td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>Caribbean, C. and S. America</td>
<td>EBV or CMV</td>
<td>30 to 50 d</td>
<td>Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly</td>
<td>Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test</td>
<td>Acetaminophen or NSAIDs, fluids</td>
</tr>
</tbody>
</table>
# Fever of Unknown Origin

## Table 29. Classification of Fever of Unknown Origin (FUO) – Temp >101°F on several occasions

<table>
<thead>
<tr>
<th>Classical FUO</th>
<th>Nosocomial FUO</th>
<th>Neutropenic FUO</th>
<th>HIV-associated FUO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &gt;3 wk</td>
<td>Hospitalized patient</td>
<td>Neutrophil count &lt;500/mL or is expected to fall to that level in 1-2 d</td>
<td>HIV infections</td>
</tr>
<tr>
<td>Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
</tr>
</tbody>
</table>

### Etiology of Classic FUO
- infectious causes (~30%)
  - TB: extra-pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - abscess: subphrenic, liver, splenic, pancreatic, perinephritic, diverticular, pelvis, psoas
  - osteomyelitis
  - bacterial endocarditis (culture negative)
  - uncommon: viral (CMV, EBV), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- neoplastic causes (~20%)
  - most commonly lymphomas (especially non-Hodgkin’s) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - solid tumors: RCC (most common), also breast, liver (hepatoma), colon, pancreas, or liver metastases
- collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still’s disease
- miscellaneous (~20%)
  - drugs, factitious fever
  - sarcoidosis, granulomatous hepatitis, IBD
  - hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - venous thromboembolic disease: PE, DVT
  - endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- unknown in 30-50% despite detailed workup

### Approach to Classic FUO
- careful history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- initial investigations as appropriate
  - blood work: CBC and differential, electrolytes, BUN, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis (SPEP), blood smear
  - cultures: blood (x2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
  - serology: HIV, monospot, CMV IgM
  - imaging: CXR, abdominal imaging
- if there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established
- if no diagnosis with the above, consider empiric therapy vs. watchful waiting
- without intervention: patients that remain undiagnosed despite extensive workup have good prognosis

---

### Anti-Drugs that may Cause Fever:
- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimalarials)
- Anti-hypertensives (hydralazine, methyl dopa)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arythmics (quinine, procainamide)
- Anti-inflammatory (NSAIDs)
- Anti-thyroid (ASA)

### Causes of Nosocomial FUO
- B, C, D, E
  - Bacterial and fungal infections of respiratory tract and surgical sites
  - Catheters (intravascular and urinary)
  - Drugs
  - Emboli

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**Anti-Drugs that may Cause Fever:**
- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimalarials)
- Anti-hypertensives (hydralazine, methyl dopa)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arythmics (quinine, procainamide)
- Anti-inflammatory (NSAIDs)
- Anti-thyroid (ASA)
Infections in the Immunocompromised Host

- Immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent.
- Type of immunosuppression predicts probable spectrum of agents.

Factors that Compromise the Immune System

- General: age (very young or elderly), malnutrition.
- Immune disease: HIV/AIDS, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia.
- DM.
- Iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g., in transplant patients).

Factors that Compromise the Immune System

<table>
<thead>
<tr>
<th>Type</th>
<th>Conditions</th>
<th>Vulnerable To</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-Mediated Immunity</td>
<td>HIV, Hodgkin's, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome</td>
<td>Latent viruses, Fungi, Parasites</td>
</tr>
<tr>
<td>Humoral Immunity</td>
<td>CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome</td>
<td>Encapsulated organisms (S. pneumoniae, H. influenzae, N. meningitidis, Salmonella typhi, GBS)</td>
</tr>
<tr>
<td>Neutrophil Function</td>
<td>Myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease</td>
<td>Catalase-producing organisms (Staphylococcus, Serratia, Nocardia, Aspergillus)</td>
</tr>
</tbody>
</table>

Febrile Neutropenia

Definition

- Fever (≥101°F/38.3°C or ≥100.4°F/38.0°C for ≥1 h) and one of:
  - ANC <0.5 OR
  - ANC <1.0 but trending down to 0.5

Pathophysiology

- Decreased neutrophil production
- Marrow: infection, aplastic/myelophthsic anemia, leukemia, lymphoma, myelodysplastic syndromes
- Iatrogenic: cancer chemotherapy, radiation, drugs
- Deficiencies: vitamin B12, folate
- Increased peripheral neutrophil destruction
- Autoimmune: Felty's syndrome, SLE, antineutrophil antibodies
- Splenic sequestration

Epidemiology/Etiology

- Most common life-threatening complication of cancer therapy
- 8 cases per 1,000 cancer patients per year in the U.S.
- Causative organism identified only 1/3 of the time
- GN (especially Pseudomonas) historically most common
- GP more common now
- Fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially Candida, Aspergillus)

Investigations

- Examine for potential sites of infection: mucositis and line infections are most common
- Do NOT perform DRE; examine perianal region
- Blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and NP swab for respiratory viruses
- CBC and differential, Cr, BUN, electrolytes, AST/ALT, total bilirubin

Treatment

- Most hospitals have their own specific protocol; one example is presented below.
Infections in Solid Organ Transplant Recipients

- Infection is a leading cause of early morbidity/mortality in transplant recipients
- Infection depends on degree of immunosuppression
  - Common infections <1 mo post-transplant
    - Bacterial infection of wound/lines/lungs, herpetic stomatitis
  - Common infections >1 mo post-transplant
    - Viral (especially CMV, EBV, VZV)
    - Fungal (especially Aspergillus, Cryptococcus, P. jiroveci)
    - Protozoan (especially Toxoplasma)
    - Unusual bacterial/mycobacterial infections (especially TB, Nocardia, Listeria)

Prophylactic Vaccinations Given Before Transplant
- To all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B vaccines
- If low titer or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 wk later)

Immune Reconstitution Syndrome

Definition
- A harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

Etiology
- Paradoxical worsening of a successfully or partially treated opportunistic infection
- New onset response to a previously unidentified opportunistic infection
- The majority of cases are in HIV/AIDS or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation
- Can occur in response to multiple infections
  - Mycobacteria (tuberculosis, avium complex)
  - Cryptococcus
  - Pneumocystis
  - Toxoplasma
  - HBV and HCV
  - Herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Molluscum contagiosum
• clinical features are dependent on the type and location of the pre-existing infection
• thought to be worse with quick increase in CD4 count and with lower pre-treatment CD4 count
• non-HIV conditions with documented IRS: solid organ transplant recipients, post-partum women, neutropenic patients, anti-TNF therapy

**Epidemiology**
• in HIV patients starting HAART, IRS reported to affect ~10%

**Investigations**
• diagnosis of exclusion
• rule out drug reaction, patient non-adherence, drug resistance

**Treatment**
• continue HAART therapy in HIV patients with mild-moderate symptoms, but consider discontinuation if symptoms are life-threatening or potentially irreversible
• treat underlying infection; initiate treatment for some infections prior to HAART initiation
• consider starting corticosteroids/NSAIDs to decrease inflammatory response

---

**A Simplified Look at Antibiotics**

• general overview, see Table 31 for more details

1. **Penicillins** (most *Streptococcus, N. meningitidis*, many oral anaerobes except *B. fragilis*)

   - Penicillin G (IV)/Penicillin V (PO)
   - Ampicillin (IV)/Amoxicillin (PO) + Enterococcus and HiPLESS*
   - Cloxacillin + MSSA but ↓ Streptococci
   - Amoxicillin-clavulanate + Pseudomonas and Enterobacter
   - Piperacillin + Pseudomonas and Enterobacter
   - Piperacillin/tazobactam

*HiPLESS = H. influenzae, Proteus, Listeria, E. coli, Salmonella, Shigella

**Figure 19. Penicillins**

2. **Cephalosporins (PO/IV)**
   • 1st generation: cephalexin/cefazolin (mostly GP, some GN)
   • 2nd generation: cefuroxime/cefprozil (some GP and some GN, *anaerobes*)
   • 3rd generation: cefixime/cefotaxime, ceftriaxone (good *Streptococcal* coverage, mostly GN) and ceftazidime (no GP, mostly GN, *Pseudomonas*)
   • 4th generation: --/cefepine (most GP, most GN, *Pseudomonas*)

3. **Aminoglycosides (GN aerobic bacilli)**
   • gentamicin
   • tobramycin
   • amikacin

4. **Macrolides (GP, *Haemophilus*, and atypical bacteria [*Legionella, Chlamyphila, Mycoplasma]*)
   • erythromycin
   • clarithromycin
   • azithromycin

5. **Fluoroquinolones (GN – although resistance becoming a huge problem)**
   • ciprofloxacin (+ *Pseudomonas*)
   • norfloxacin (for UTI only)
   • respiratory fluoroquinolones (some GP, GN, "atypicals", *Legionella, Mycoplasma, Chlamyphila*)
     - levofloxacin
     - moxifloxacin (+ anaerobes)

6. **Carbapenems (broad coverage: GP, GN, and anaerobes)**
   • imipenem (+ *Pseudomonas*)
   • meropenem (+ *Pseudomonas*)
   • ertapenem
7. Others
- doxycycline/tetracycline (GP, syphilis, Chlamyphila, Rickettsia, Mycoplasma)
- vancomycin (all GP and C. difficile – the oral form)
- linezolid (for resistant GP infections)
- clindamycin (most GP, GN anaerobes)
- TMP/SMX (most S. aureus including: MRSA, GN aerobes, Pneumocystis)
- nitrofurantoin (GN bacilli, S. saprophyticus, Enterococcus)
- metronidazole (anaerobes including: C. difficile, Trichomonas, Entamoeba)
- treatment for C. difficile: metronidazole OR oral vancomycin; consider both in serious infection

Antimicrobials

Antibiotics

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S
    - if causative organism identified, use antibiotic to which organism is sensitive
    - if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy
    - (and continue with empiric antibiotic(s) if indicated)

Reasons for Combination Therapy
- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. Enterococcus spp. causing endocarditis)
- To prevent emergence of resistance

Bactericidal Antibiotics  Bacteriostatic Antibiotics
"Very Finely Proficient At CCell Murder"  "ECSTaTIC"
Vancomycin  Erythromycin (and other macrolides)
Fluoroquinolones  Chloramphenicol
Penicillin  Sulfamethaxazole
Aminoglycosides  Trimethoprim
Cephalosporins  Tetracyclines
Carbapenems  Metronidazole

Figure 20. Mechanism of action of antibiotics
## Table 31. Antibiotics

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL WALL INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Benzyl penicillin - penicillin G IV/IM - penicillin V PO</td>
<td>GP except Staphylococcus, Enterococcus Oral anaerobes</td>
<td>Bactericidal: β-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBPs) preventing cross-linking of peptidoglycan</td>
<td>Immediate allergy (lgE): anaphylaxis, urticaria Late-onset allergy (lgG): urticaaria, rash, serum sickness Interstitial nephritis Dose related toxicity: seizures Diarrhea</td>
<td>Mild to moderately severe infections caused by susceptible organisms including actinomycosis, streptococcal pharyngitis, sinusitis, abdominal and pelvic infections, pneumococcal pneumonia, syphilis</td>
<td>Hypersensitivity to penicillin</td>
</tr>
<tr>
<td>Aminopenicillin - ampicillin IV - amoxicillin PO (Moxatag™)</td>
<td>Same as penicillin AND Enterococcus Listeria</td>
<td>See above</td>
<td>See above</td>
<td>Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (ADOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for H. pylori treatment, Lyme disease, pneumococcal pneumonia; URI (amoxicillin and ampicillin) for most enterococci and susceptible gram-negative pathogens</td>
<td>Hypersensitivity to penicillin or β-lactam antibiotics</td>
</tr>
<tr>
<td>ISOXAZOLYL penicillin - cloxacillin - methicillin - nafcillin - oxacillin</td>
<td>Methicillin-sensitive Staphylococcus aureus; streptococci</td>
<td>See above</td>
<td>See above</td>
<td>Bacterial infections caused by staphylococci and streptococci including skin soft-tissue infections</td>
<td>Hypersensitivity to cloxacillin or any penicillin</td>
</tr>
<tr>
<td>β-lactam/β-lactamase inhibitor combinations - amoxycillin-clavulanate (Amoclan®) - Augmentin® - piperacillin/tazobactam (Zosyn®)</td>
<td>Same as penicillin AND Staphylococcus H. influenzae Enterococcus Anaerobes (oral and gut)</td>
<td>β-lactamases produced by certain bacteria inactivate β-lactams Lactamase inhibitors prevent this process, preserving antibacterial effect of β-lactams</td>
<td>See above</td>
<td>Various β-lactamase producing bacteria, Clavulin® sensitive bacteria including RTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections</td>
<td>Hypersensitivity to penicillin or cephalosporin History of Clavulin®-associated jaundice or hepatic dysfunction</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>PO</td>
<td>1° cephalaxin (Bexil®)</td>
<td>IV</td>
<td>Cefazolin</td>
<td>GP Good with the exception of Enterococcus and MRSA</td>
<td>E. coli, Klebsiella, Proteus, H. influenzae (not all isolates)</td>
</tr>
<tr>
<td>2° cefuroxime (Ceftin®) ceftriaxol</td>
<td>Cefuroxime (Zinacef®) cefotaxim</td>
<td>Weaker activity than 1°</td>
<td>More coverage than 1° Includes anaerobes</td>
<td>See above</td>
<td>See above</td>
</tr>
<tr>
<td>3° cefixime (Suprax®)</td>
<td>Cefixime (Suprax®) Clavulanate (Clavam®) cefotaxim (Fortaz®)</td>
<td>S. aureus + streptococcal coverage (cefotaxime and ceftriaxone) especially S. pneumoniae</td>
<td>Broad coverage Includes Pseudomonas for cefotaxime only</td>
<td>See above</td>
<td>~1% penicillin allergy cross-reactivity</td>
</tr>
<tr>
<td>4° ceftzepine (Maxipen®)</td>
<td>Broad spectrum</td>
<td>Broad coverage including Pseudomonas</td>
<td>See above</td>
<td>See above</td>
<td>Empiric therapy for febrile neutropenia</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
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<th>Contraindications</th>
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<td></td>
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<tr>
<td><strong>Carbapenems</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>imipenem (Primaxin®)</td>
<td>GP except MRSA, + Enterobacter, ESBLs, anaerobes</td>
<td>β-lactam inhibits PBP and prevents cross-linking of peptidoglycan</td>
<td>Penicillin allergy cross-reactivity, seizures</td>
<td>Treatment of infections caused by GNB producing extended-spectrum β-lactamases, serious infections caused by susceptible organisms</td>
<td>Hypersensitivity to imipenem</td>
</tr>
<tr>
<td>meropenem (Merrem®)</td>
<td>See above; does not cover Enterococcus</td>
<td>See above</td>
<td>See above</td>
<td>See above; once-daily administration makes it convenient for outpatient IV therapy</td>
<td>Hypersensitivity to β-lactams</td>
</tr>
<tr>
<td>ertapenem (INVanz®)</td>
<td>GP except Enterococcus, MRSA, anaerobes</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Hypersensitivity to β-lactams</td>
</tr>
<tr>
<td><strong>Glycopeptides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td>GP including MRSA, not VRE, C. difficile if PO</td>
<td>Glycopeptide sterically inhibits cell wall synthesis</td>
<td>Red Man Syndrome, Nephrotoxicity, Ototoxicity, Thrombocytopenia</td>
<td>Severe or life-threatening GPs, patients with β-lactam allergy</td>
<td>Hypersensitivity to vancomycin</td>
</tr>
<tr>
<td><strong>PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>erythromycin (EryPed®)</td>
<td>GP except Enterococcus, GN, Legionella, B. pertussis, “Atypicals”: Chlamydia, Mycoplasma</td>
<td>Binds to 50S ribosomal subunit inhibiting protein synthesis</td>
<td>GI upset, Acute cholestatic hepatitis, Prolonged QT</td>
<td>Susceptible RTI, pertussis, diphtheria, Legionnaires’ disease, skin and soft tissue infections</td>
<td>Hypersensitivity to erythromycin, Concurrent therapy with astemizole, terfenadine</td>
</tr>
<tr>
<td>clarithromycin (Biaxin®)</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for H. pylori treatment</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td>azithromycin (Zithromax®)</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, Campylobacter infections if treatment indicated, chlamydia</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td><strong>Lincosamides</strong></td>
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<td></td>
</tr>
<tr>
<td>clindamycin (Cleocin®)</td>
<td>GP except Enterococcus, MRSA, Anaerobes</td>
<td>Inhibits peptide bond formation at 50S ribosome</td>
<td>Pseudomembranous colitis, GI upset</td>
<td>Treatment of suspected or proven infections caused by GP, anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections</td>
<td>Hypersensitivity to clindamycin, Infants &lt;30 d</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>GP, GN, Anaerobes</td>
<td>Inhibits peptidyl transferase action of tRNA at 50S ribosome</td>
<td>Aplastic anemia, Gray Baby Syndrome</td>
<td>Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to β-lactams</td>
<td>Hypersensitivity to chloramphenicol</td>
</tr>
<tr>
<td>linezolid (Zyvox®)</td>
<td>GP including VRE + MRSA</td>
<td>Binds 50S ribosome and prevents functional 70S initiation complex</td>
<td>HTN (acts as MAOI), Risks with prolonged use: myelosuppression, optic neuropathy, peripheral neuropathy</td>
<td>Vancomycin-resistant Enterococcus faecium infections including intra-abdominal, skin and skin-structure, and urinary tract infections, MRSA infections as outpatient therapy</td>
<td>Hypersensitivity to linezolid</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

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<tr>
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</thead>
<tbody>
<tr>
<td><strong>PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
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</tr>
<tr>
<td>gentamicin, tobramycin, amikacin (Amikin®)</td>
<td>GN (includes Pseudomonas)</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>Nephrotoxicity (reversible), Vestibular and ototoxicity (irreversible)</td>
<td>GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections</td>
<td>Pre-existing hearing loss and renal dysfunction</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
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<tr>
<td>tetracycline, minocycline (Minocin®), doxycycline (Adoxa®)</td>
<td>GP, Anaerobes, &quot;Atypicals&quot;: Chlamyphila, Mycoplasma, Rickettsia, Borrelia burgdorferi, Treponema</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>GI upset, Hepatotoxicity, Fanconi’s syndrome, Photosensitivity, Teratogenic, Yellow teeth and stunted bone growth in children</td>
<td>Rickettsial infections, Chlamyphila, acne, PID (step-down), malaria prophylaxis (doxycycline)</td>
<td>Severe renal or hepatic dysfunction, Pregnancy or lactation, Children under 8 yr</td>
</tr>
<tr>
<td><strong>TOPOISOMERASE INHIBITORS</strong></td>
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<tr>
<td>Fluoroquinolones (FQs)</td>
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<tr>
<td>ciprofloxacin (Cipro®), norfloxacin (Noroxin®), ofloxacin</td>
<td>Poor GP activity, GN (includes Pseudomonas), Atypicals, Moxifloxacin also covers many anaerobes</td>
<td>Inhibits DNA gyrase</td>
<td>H/A, dizziness, Allergy, Seizures, Prolonged QT, Dysglycemia (levofloxacin, moxifloxacin)</td>
<td>Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin), bone and joint infections with aracillin-clavulanate low management of ‘low-risk’ febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td>levofloxacin (Levaquin®), moxifloxacin (Avelox®)</td>
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<tr>
<td>Rifampin</td>
<td>GP cocci, N. meningitidis, H. influenzae, Mycobacteria</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatic dysfunction, P450 enzyme induction, Orange tears/saliva/urine</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with N. meningitidis or HiB meningitis</td>
<td>Jaundice, Not to be used as monotherapy (except for prophylaxis)</td>
</tr>
<tr>
<td>Metronidazole (Flagyl®)</td>
<td>Anaerobes, Protozoa</td>
<td>Forms toxic metabolites in bacterial cell which damage microbial DNA</td>
<td>Disulfiram-type reaction with EtOH, Seizures, Perihiperal neuropathy</td>
<td>Protozoal infections (trichomoniasis, amebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections</td>
<td></td>
</tr>
<tr>
<td><strong>ANTI-METABOLITE</strong></td>
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<tr>
<td>Trimethoprim-Sulfamethoxazole (TMP-SMX) (Septra®, Bactrim®)</td>
<td>GP, especially S. aureus (including most MRSA), GN: enteric, Other: Pneumocystis, Toxoplasmosis</td>
<td>Inhibits folic acid pathway (TMP inhibits DHFR and SMX competes with PABA)</td>
<td>Hepatitis Stevens-Johnson syndrome, Bone marrow suppression, Hyperkalemia, Drug toxicity (increases free levels of many drugs, including glyburide, warfarin)</td>
<td>Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of P. jiroveci pneumonia</td>
<td>Hypersensitivity to TMP-SMX, sulfa drugs</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-METABOLITE</strong></td>
<td></td>
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</tr>
<tr>
<td>Nitrofurantoin (Macrobid®, Macrodantin®)</td>
<td>Enterococcus, S. saprophyticus, GN (califorms)</td>
<td>Reactive metabolites inhibit ribosomal protein synthesis</td>
<td>Cholestasis, hepatitis</td>
<td>Lower UTI; not pyelonephritis or bacteremia</td>
<td>Hyper-sensitivity to nitrofurantoin or pregnant patients during labor and delivery or when labor imminent infants &lt; 1 mo of age</td>
</tr>
<tr>
<td><strong>ANTI-MYCOBACTERIALS</strong></td>
<td></td>
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</tr>
<tr>
<td>Isoniazid (INH)</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Hepatotoxicity Heme: neutropenia, thrombocytopenia, anemia</td>
<td>Part of multidrug treatment for active TB</td>
<td>Drug-induced hepatitis or acute liver disease</td>
</tr>
<tr>
<td>Rifampin (RIF)</td>
<td>Mycobacteria</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatotoxicity, P450 enzyme inducer</td>
<td>Part of multidrug treatment for active TB</td>
<td>Jaundice Not to be used monotherapy (except for prophylaxis)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Loss of color vision</td>
<td>Part of multidrug treatment for active TB</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Pyrazinamide (PZA)</td>
<td>Mycobacteria</td>
<td>Unknown</td>
<td>Hepatotoxicity</td>
<td>Part of multidrug treatment for active TB</td>
<td>Severe hepatic damage or acute liver disease Patients with acute gout</td>
</tr>
<tr>
<td><strong>SULFONES</strong></td>
<td></td>
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</tr>
<tr>
<td>Dapsone</td>
<td>M. leprae, P. jiroveci, Toxoplasma</td>
<td>Inhibit folic acid synthesis by competition with PABA</td>
<td>Rash Drug fever</td>
<td>Part of multidrug treatment for M. leprae, part of treatment for P. jiroveci pneumonia (with TMP), P. jiroveci pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine</td>
<td></td>
</tr>
</tbody>
</table>

### Table 32. Antibiotics for Selected Bacteria

<table>
<thead>
<tr>
<th>Pseudomonas</th>
<th>S. aureus</th>
<th>Enterococcus</th>
<th>H. influenzae</th>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>Gentamicin, Tobramycin</td>
<td>Cefazidime</td>
<td>Metronidazole</td>
<td></td>
</tr>
<tr>
<td>Gentamicin, Tobramycin</td>
<td>Piperacillin-tazobactam</td>
<td>Cefepime</td>
<td>Clindamycin</td>
<td></td>
</tr>
<tr>
<td>Cefazidime</td>
<td>Imipenem</td>
<td>Piperacillin-tazobactam</td>
<td>Amoxicillin-clavulanate</td>
<td></td>
</tr>
</tbody>
</table>

### Table 33. Antivirals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-HERPESVIRUS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Acyclovir, Valacyclovir (Valtrex®) (prodrug of acyclovir)</td>
<td>HSV-1,2, VZV</td>
<td>Guanosine analog inhibits viral DNA polymerase</td>
<td>PO well-tolerated IV: nephrotoxicity, CNS</td>
<td>Hypersensitivity to acyclovir or valacyclovir</td>
</tr>
<tr>
<td>Famiclovir (Famvir®)</td>
<td>HSV-1,2, VZV</td>
<td>See above</td>
<td>H/A, nausea</td>
<td>Hypersensitivity to famclovir or penciclovir</td>
</tr>
<tr>
<td>Ganciclovir (Cytovene®) (prodrug of ganciclovir)</td>
<td>CMV, HSV-1,2, VZV</td>
<td>See above</td>
<td>Hem, neutropenia, thrombocytopenia, anemia</td>
<td>Hypersensitivity to ganclovir or valganclovir Possible cross-hypersensitivity between acyclovir and valacyclovir</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>CMV, Acyclovir-resistant HSV, VZV</td>
<td>Pyrophosphate analog inhibits viral DNA polymerase</td>
<td>Nephrotoxicity Anemia, Electrolyte disturbances</td>
<td>Hypersensitivity to foscarnet</td>
</tr>
</tbody>
</table>
### Table 33. Antivirals (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTHER ANTIVIRALS</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>(pegylated) interferon-α-2a or -2b</td>
<td>Chronic hepatitis B or C</td>
<td>Inhibits viral protein synthesis</td>
<td>“Flu-like” syndrome Depression Bone marrow suppression</td>
<td>Hypersensitivity to any interferon Cannot use in combination with ribavirin if renal impairment</td>
</tr>
<tr>
<td></td>
<td>HPV</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ribavirin (Virazole™)</td>
<td>Chronic hepatitis C</td>
<td>Guanosine analog with multiple postulated mechanisms of action</td>
<td>Hemolytic anemia Rash, conjunctivitis Highly teratogenic</td>
<td>Pregnancy, women who may become pregnant or their partners Renal impairment</td>
</tr>
<tr>
<td></td>
<td>RSV</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Lassa fever</td>
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<tr>
<td>lamivudine (Epivir™)</td>
<td>Chronic hepatitis B</td>
<td>See HIV and AIDS, ID29</td>
<td>Hypersensitivity to lamivudine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Neuraminidase inhibitors:</strong></td>
<td>Influenza A and B: treatment and prophylaxis</td>
<td>Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation</td>
<td>GI: N/V, diarrhea Bronchospasm in zanamivir</td>
<td>Hypersensitivity to the neuraminidase inhibitors</td>
</tr>
<tr>
<td>zanamivir (Relenza™)</td>
<td></td>
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<tr>
<td>oseltamivir (Tamiflu™)</td>
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</table>

### Table 34. Antifungals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLYENES</strong></td>
<td></td>
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<tr>
<td>amphotericin B</td>
<td>Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis Pulmonary: Aspergillosis CNS: Cryptococcus</td>
<td>A polyene antimicrobial: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death</td>
<td>Nephrotoxicity Hypo/hyperkalemia Infusion reactions: chills, fevers, H/A Peripheral phlebitis</td>
<td>Renal impairment</td>
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<td></td>
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<tr>
<td>nystatin (oral, topical)</td>
<td>Candidiasis: mucocutaneous, GI, oral (thrush), vaginal</td>
<td>See above Not absorbed from the GI tract</td>
<td>GI: N/V, diarrhea Highly toxic if given IV</td>
<td></td>
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<tr>
<td><strong>IMIDAZOLES</strong></td>
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</tr>
<tr>
<td>clotrimazole (Alevazol™, Lotrimin™)</td>
<td>Oral and vulvovaginal candidiasis Dermatomycoses</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Pruritis, skin irritation</td>
<td></td>
</tr>
<tr>
<td>miconazole (Vagistat-3™, Desenex™)</td>
<td>Vulvovaginal candidiasis Dermatomycoses</td>
<td>Vaginal burning N/V</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketoconazole (Nizoral™)</td>
<td>Dermatomycoses Seborrheic dermatitis</td>
<td>Pruritis, skin irritation GI nonspecific Results in decreased androgen and testosterone synthesis</td>
<td>Coss-sensitivity with other azoles possible Hepatic dysfunction Pregnant women or those that may become pregnant</td>
<td></td>
</tr>
</tbody>
</table>
### Table 34. Antifungals (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRIAZOLES</strong></td>
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<tr>
<td>fluconazole</td>
<td>Candida infections (mucosal and invasive)</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Elevated liver enzymes GI nonspecific</td>
<td>Cross-sensitivity with other azoles unknown</td>
</tr>
<tr>
<td>(Diflucan®)</td>
<td>Cryptococcal meningitis (step-down therapy)</td>
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<tr>
<td>itraconazole</td>
<td>Sporotrichosis</td>
<td></td>
<td>Elevated liver enzymes Rash GI nonspecific HTN Hyperkalemia Peripheral edema</td>
<td>Cross-sensitivity with other azoles unknown Severe ventricular dysfunction</td>
</tr>
<tr>
<td>(Sporanox®)</td>
<td>Onychomycoses Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis</td>
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<tr>
<td>voriconazole</td>
<td>Aspergillosis Candidiasis</td>
<td>Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma with long-term use in immunosuppressed patients Prolonged QT Periostitis Neurologic toxicity</td>
<td>Cross-sensitivity with other azoles unknown May avoid or alter doses if co-administered with other CYP3A4 substrates, rifampin, carbamazepine, long-acting barbiturates, ritonavir, efavirenz, sirolimus, rifabutin, ergot alkaloids</td>
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<tr>
<td>(Vfend®)</td>
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<tr>
<td>posaconazole</td>
<td>Candidiasis</td>
<td></td>
<td>Elevated liver enzymes H/A Prolonged QT</td>
<td>Coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus</td>
</tr>
<tr>
<td>(Posanol®, Noxafil®)</td>
<td>Aspergillosis Mucormycosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ALLYLAMINES</strong></td>
<td></td>
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</tr>
<tr>
<td>terbinafine</td>
<td>Dermatomycoses Onychomycoses</td>
<td>Inhibits enzyme needed for ergosterol synthesis</td>
<td>Rash, local irritation GI nonspecific, transaminits</td>
<td>Active liver disease</td>
</tr>
<tr>
<td>(Lamisil®)</td>
<td></td>
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<tr>
<td><strong>ECHINOCANDINS</strong></td>
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<tr>
<td>caspofungin</td>
<td>Refractory aspergillosis, candidemia (azole-resistant)</td>
<td>Inhibits 1-3 β-D-glucan synthesis (needed for fungal cell wall)</td>
<td>Hepatotoxicity Infusion and injection site reactions</td>
<td></td>
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<tr>
<td>micafungin</td>
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<tr>
<td>anidulafungin</td>
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</tbody>
</table>
Table 35. Antiparasitics

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIMALARIALS</strong></td>
<td></td>
<td></td>
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<tr>
<td>chloroquine</td>
<td>Malaria: treatment of erythrocytic phase of all five species of Plasmodium that infect humans</td>
<td>Inhibits parasite heme polymerase</td>
<td>CNS: blurred vision, retinopathy, dizziness Non-specific GI (rare with prophylaxis)</td>
<td>Hypersensitivity to chloroquine or other 4-aminoquinoline Retinal or visual field changes due to 4-aminoquinoline</td>
</tr>
<tr>
<td>quinine</td>
<td>Malaria: treatment of all five species of Plasmodium that infect humans, including chloroquine-resistant P. falciparum</td>
<td></td>
<td>Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (N/V, diarrhea), CNS (H/A, fever) Hypoglycemia</td>
<td>Hypersensitivity to quinine, may have cross-sensitivity with quinidine Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use</td>
</tr>
<tr>
<td>mefloquine (Lariam®)</td>
<td>Malaria: treatment and prophylaxis of all four species of Plasmodium that infect humans</td>
<td>Interferes with mitochondrial function</td>
<td>CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, H/A</td>
<td>History of seizures, psychosis, severe anxiety or depression</td>
</tr>
<tr>
<td>primaquine</td>
<td>Malaria: treatment of liver hypnozoites of P. vivax and P. ovale; prophylaxis of all Plasmodium spp. Pneumocystis jiroveci (with clindamycin)</td>
<td>Inhibits mitochondrial electron transport and dihydrofolate reductase</td>
<td>Hemolytic anemia in G6PD deficient GI upset (take with food)</td>
<td>GI nonspecific G6PD deficiency Concurrent or recent use of quinacrine Pregnancy</td>
</tr>
<tr>
<td>atovaquone/proguanil (Malarone®)</td>
<td>Malaria: treatment and prophylaxis of P. falciparum</td>
<td></td>
<td>N/V, anorexia, diarrhea, abdominal pain (take with food)</td>
<td>Hypersensitivity to atovaquone or proguanil Severe renal impairment</td>
</tr>
<tr>
<td>artesinin derivatives (artemeter, artemate, etc.) Note: marketed primarily in endemic countries</td>
<td>Malaria: treatment of all Plasmodium species Severe malaria (IV artesunate) Typically used in combination with a longer-acting agent from above</td>
<td>Binds iron, leading to formation of free radicals that damage parasite proteins</td>
<td>Transient neurologic deficits (nystagmus, balance disturbance) Transient neutropenia (at high doses of oral artesunate)</td>
<td>Hypersensitivity to artesminins</td>
</tr>
</tbody>
</table>
### Table 35. Antiparasitics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OTHER ANTI-PROTOZOAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iodoquinol (Yodoxin®)</td>
<td>Amoebiasis: E. histolytica, Dientamoeba fragilis, Balantidium coli, Blastocystis hominis</td>
<td>Contact amoecide that acts in intestinal lumen by uncertain mechanism</td>
<td>GI: N/V, diarrhea, abdominal pain CNS: H/A, seizures, encephalitis</td>
<td>Hypersensitivity to any 8-hydroxy-quinoline or iodine Patients with hepatic damage or optic neuropathy Pregnancy</td>
</tr>
<tr>
<td>metronidazole</td>
<td>Amoebiasis, T. vaginalis, giardiasis</td>
<td>See Antibiotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitazoxanide</td>
<td>Cryptosporidium, giardiasis</td>
<td>Interferes with parasite anaerobic metabolism</td>
<td>N/V, diarrhea, abdominal pain, H/A</td>
<td>Hypersensitivity to nitazoxanide</td>
</tr>
<tr>
<td><strong>ANTI-HELMINTHICS</strong></td>
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<td></td>
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</tr>
<tr>
<td>praziquantel</td>
<td>Schistosomiasis and other flukes Tapeworms</td>
<td>Increases Ca$^{2+}$ permeability of helminth cell membrane, causing paralysis and detachment</td>
<td>N/V, fever, diziness</td>
<td>Ocular cysticercosis</td>
</tr>
<tr>
<td>albendazole</td>
<td>Intestinal roundworms Neurocysticercosis Microsporidiosis Echinococcus → Hydatid disease</td>
<td>Inhibits glucose uptake into susceptible parasites</td>
<td>Elevated liver enzymes Alopecia GI nonspecific Agranulocytosis</td>
<td>Pregnancy Ocular cysticercosis or intraventricular cysticercosis</td>
</tr>
<tr>
<td>ivermectin</td>
<td>Strongyloidiases Onchocerciasis Scabies</td>
<td>Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis</td>
<td>Nausea, bloating, diarrhea, myalgias, lightheadedness, H/A</td>
<td>Hypersensitivity to ivermectin Pregnancy</td>
</tr>
<tr>
<td>diethylcarbamazine</td>
<td>Wuchereria bancrofti Loa loa</td>
<td></td>
<td>Anorexia, N/V, H/A, drowsiness, encephalitis, retinal hemorrhage Mazzotti reaction if coinfected with onchocerciasis</td>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

### Quick Reference: Common Infections and Their Antibiotic Management

#### Table 36. Common Infections and Their Empiric Antibiotic Management

<table>
<thead>
<tr>
<th>Infection</th>
<th>Bacteria</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Community-acquired</td>
<td>S. pneumonia, H. influenzae, M. catarrhalis, Mycoplasma, Chlamydophila, Legionella, S. aureus</td>
<td>Outpatient: amoxicillin-clavulanate OR doxycycline Hospitalized: antipseudomonal respiratory fluoroquinolone OR 3rd generation cephalosporin ± macrolide</td>
</tr>
<tr>
<td>• Hospital-acquired</td>
<td>GNB (including Pseudomonas in special settings such as ICU)</td>
<td>ceftriaxone (if not at risk for Pseudomonas) OR piperacillin/tazobactam OR meropenem</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>Mycobacterium tuberculosis</td>
<td>isoniazid + rifampin + pyrazinamide + ethambutol + pyridoxine (for initial empiric therapy)</td>
</tr>
<tr>
<td><strong>UTI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>KEEPS</td>
<td>fluoroquinolone OR TMP/SMX OR nitrofurantoin</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>KEEPS</td>
<td>ciprofloxacin OR 3rd generation cephalosporin</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Neisseria gonorrhoeae Chlamydia</td>
<td>ceftriaxone azithromycin OR doxycycline</td>
</tr>
<tr>
<td><strong>SOFT TISSUE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>β-hemolytic streptococci, MSSA</td>
<td>cephalaxin OR cefazolin</td>
</tr>
<tr>
<td>Necrotizing Fasciitis</td>
<td>Type I: polymicrobial (GNB and anaerobes)</td>
<td>piperacillin/tazobactam + clindamycin</td>
</tr>
<tr>
<td></td>
<td>Type II: β-hemolytic streptococci Unknown organism(s)</td>
<td>penicillin G + clindamycin</td>
</tr>
</tbody>
</table>

*KEEPS = Klebsiella, E. coli, Enterococci, Proteus mirabilis, Pseudomonas, S. saprophyticus*
### Table 36. Common Infections and Their Empiric Antibiotic Management (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Bacteria</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BONE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>MSSA</td>
<td>cloxacinil OR cefazolin</td>
</tr>
<tr>
<td>Diabetic Foot</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mild</td>
<td>MSSA, Streptococcus spp.</td>
<td>cephalaxin OR clindamycin</td>
</tr>
<tr>
<td>• Moderate or severe</td>
<td>Polymicrobial</td>
<td>clindamycin + ciprofloxacin OR piperacillin/ tazobactam ± vancomycin if MRSA suspected</td>
</tr>
<tr>
<td>Septic Arthritis</td>
<td>N. gonorrhoae (sexually active adults) S. aureus, S. pyogenes</td>
<td>vancomycin + ceftriaxone</td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>S. pneumoniae, N. meningitidis, H. influenzae</td>
<td>ceftriaxone + vancomycin (+ ampicillin for Listeria in very young, old, immunocompromised)</td>
</tr>
<tr>
<td><strong>Bacterial Endocarditis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Native valve</td>
<td>S. viridans, S. aureus, Enterococcus</td>
<td>Usually non-urgent and can wait for confirmation of etiology Empiric therapy if patient unstable, vancomycin + gentamicin OR ceftriaxone; take multiple blood cultures prior to initiating therapy</td>
</tr>
</tbody>
</table>

### References


Harrington LI. High yield microbiology and infectious diseases. Lippincott Williams & Wilkins, 2000.


**Neurological Infections**


**Respiratory Infections**


**Cardiac Infections**


**Gastrointestinal Infections**

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Gottlieb, T. Health CS. Diarrhea in adults (acute). Clinical Evidence 2011;02:301.


Thielman NM, Guerraert RL. Acute infectious diarrhea. NEJM 2004;350:34-47.

**Bone and Joint Infections**


**Systemic Infections**


**Principles of Microbiology**

References

**HIV and AIDS**


**Fungal Infections**


**Parasitic Infections**


**Infections in the Immunocompromised Host**


**Fever of Unknown Origin**


**Nosocomial Infections**


**Travel Medicine**


**Antimicrobials**


**Antivirals**


# Medical Imaging

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2. **Magnetic Resonance Imaging**
3. **Positron Emission Tomography Scans**
4. **Contrast Enhancement**

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2. **Computed Tomography Chest**
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## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>18FDG</td>
<td>18-fluorodeoxyglucose</td>
</tr>
<tr>
<td>AP</td>
<td>anteroposterior</td>
</tr>
<tr>
<td>AROS</td>
<td>acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AV</td>
<td>arteriovenous</td>
</tr>
<tr>
<td>AXR</td>
<td>abdominal x-ray</td>
</tr>
<tr>
<td>BODP</td>
<td>bronchiolitis obliterans organizing pneumonia</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomographic angiogram</td>
</tr>
<tr>
<td>CVD</td>
<td>collagen vascular disease</td>
</tr>
<tr>
<td>CVP</td>
<td>central venous pressure</td>
</tr>
<tr>
<td>CR</td>
<td>chest x-ray</td>
</tr>
<tr>
<td>DEXA</td>
<td>dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>DMSA</td>
<td>dimercaptosuccinic acid</td>
</tr>
<tr>
<td>DSA</td>
<td>digital subtraction angiography</td>
</tr>
<tr>
<td>DTPA</td>
<td>diethylene triamine pentaacetic acid</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted image</td>
</tr>
<tr>
<td>ECD</td>
<td>ethyl cysteinate dimer</td>
</tr>
<tr>
<td>ERCP</td>
<td>endoscopic retrograde cholangiopancreatography</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GPA</td>
<td>granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
</tr>
<tr>
<td>HIDA</td>
<td>hepatobiliary iminodiacetic acid</td>
</tr>
<tr>
<td>HMNP0</td>
<td>hexamethylpropyleneamine oxime</td>
</tr>
<tr>
<td>HSG</td>
<td>hysterosalpingogram</td>
</tr>
<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>IVC</td>
<td>iliofemoral vein</td>
</tr>
<tr>
<td>IP</td>
<td>interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous pyelogram</td>
</tr>
<tr>
<td>LA</td>
<td>left atrium</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>MAA</td>
<td>microaggregated albumin</td>
</tr>
<tr>
<td>MAG3</td>
<td>martelidate</td>
</tr>
<tr>
<td>MRA</td>
<td>magnetic resonance angiography</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>MUGA</td>
<td>multiple gated acquisition</td>
</tr>
<tr>
<td>PA</td>
<td>posterioranterior</td>
</tr>
<tr>
<td>PBD</td>
<td>percutaneous biliary drainage</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFT</td>
<td>pulmonary function test</td>
</tr>
<tr>
<td>PEC</td>
<td>peripherally-inserted central catheter</td>
</tr>
<tr>
<td>POCUS</td>
<td>point-of-care ultrasound</td>
</tr>
<tr>
<td>PTA</td>
<td>percutaneous transluminal angioplasty</td>
</tr>
<tr>
<td>PTC</td>
<td>percutaneous transhepatic cholangiography</td>
</tr>
<tr>
<td>RA</td>
<td>right atrium</td>
</tr>
<tr>
<td>RAU</td>
<td>radioactive iodine uptake</td>
</tr>
<tr>
<td>RV</td>
<td>right ventricle</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
</tr>
<tr>
<td>SVC</td>
<td>superior vena cava</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TKN</td>
<td>tenecteplase</td>
</tr>
<tr>
<td>TPA</td>
<td>tissue plasminogen activator</td>
</tr>
<tr>
<td>TRUS</td>
<td>transrectal ultrasound</td>
</tr>
<tr>
<td>TVUS</td>
<td>transvaginal ultrasound</td>
</tr>
<tr>
<td>U/S</td>
<td>ultrasound</td>
</tr>
<tr>
<td>VCUG</td>
<td>voiding cystourethrogram</td>
</tr>
<tr>
<td>V/Q</td>
<td>ventilation/perfusion</td>
</tr>
</tbody>
</table>
**Imaging Modalities**

**X-Ray Imaging**
- x-rays, or Röentgen rays, are a form of electromagnetic energy of short wavelength
- as x-ray photons traverse matter, they can be absorbed (a process known as “attenuation”) and/or scattered
- the density of a structure determines its ability to attenuate or “weaken” the x-ray beam
  - air < fat < water < bone < metal
- structures that have high attenuation (e.g. bone) appear white on the resulting images

**Plain Films**
- x-rays pass through the patient and interact with a detection device to produce a 2-dimensional projection image
- structures closer to the film appear sharper and less magnified
- contraindications: pregnancy (relative)
- advantages: inexpensive, non-invasive, readily available
- disadvantages: radiation exposure, generally poor at distinguishing soft tissues

**Fluoroscopy**
- used for guiding angiographic and interventional procedures, in contrast examinations of the GI tract, and in the OR for certain surgical procedures (e.g. orthopedic, urological)
- on the fluoroscopic image, black and white are reversed so that bone and contrast agents appear dark and radiolucent structures appear light
- advantages: continuous x-rays allow real-time visualization
- disadvantages: increased radiation dose; however, the use of pulsed fluoroscopy has reduced fluoroscopy time by 76% and radiation dose by 64% as compared with continuous fluoroscopy

**Computed Tomography**
- x-ray beam opposite a detector moves in a continuous 360 degree arc as patient is advanced
- subsequent computer assisted reconstruction of anatomical structures from the axial plane
- attenuation is quantified in Hounsfield units
- structures are described based on their echogenicity; hyperechoic structures appear bright (ultrasound reflected) whereas hypoechoic structures appear dark (U/S waves not reflected back but pass through)
- higher U/S frequencies result in greater resolution but greater attenuation (i.e. deeper structures more difficult to visualize)
- artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (e.g. tissue/air) or absorbs (e.g. tissue/bone) sound waves; enhancement refers to the increase in reflection amplitude (i.e. increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
- Doppler: determines the velocity of blood flowing past the transducer based on the Doppler effect
- duplex scan: Doppler + visual images
- advantages: relatively low cost, non-invasive, no radiation, real time imaging, may be used for guided biopsies, many different imaging planes (axial, sagittal), determines cystic vs. solid
- disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus

**Ultrasound**
- high frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
- reflection (or “echo”) occurs when the sound waves pass through tissue interfaces of different acoustic densities
- structures are described based on their echogenicity; hyperechoic structures appear bright (ultrasound reflected) whereas hypoechoic structures appear dark (U/S waves not reflected back but pass through)
- higher U/S frequencies result in greater resolution but greater attenuation (i.e. deeper structures more difficult to visualize)
- artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (e.g. tissue/air) or absorbs (e.g. tissue/bone) sound waves; enhancement refers to the increase in reflection amplitude (i.e. increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
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- disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus

**Attenuation**
- Bone (= bright) > gray matter > white matter (“fatty” myelin) > CSF > air (= dark)

**Typical Effective Doses from Diagnostic Medical Exposures**

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Equivalent Number of Chest X-Rays</th>
<th>Approximate Equivalent Period of Natural Background Radiation (~23 mSv/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>5</td>
<td>12 d</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>10</td>
<td>3 wk</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>50</td>
<td>4 m</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>75</td>
<td>6 m</td>
</tr>
<tr>
<td>Chest (single PA/im)</td>
<td>1</td>
<td>2 d</td>
</tr>
<tr>
<td>Shoulder</td>
<td>0.5</td>
<td>1 d</td>
</tr>
<tr>
<td>Mammography</td>
<td>20</td>
<td>7 wk</td>
</tr>
<tr>
<td>Abdomen</td>
<td>35</td>
<td>3 m</td>
</tr>
<tr>
<td>Hip</td>
<td>35</td>
<td>3 m</td>
</tr>
<tr>
<td>Pelvis</td>
<td>30</td>
<td>10 wk</td>
</tr>
<tr>
<td>Knee</td>
<td>0.25</td>
<td>&lt;1 d</td>
</tr>
<tr>
<td>IVU</td>
<td>150</td>
<td>1 yr</td>
</tr>
<tr>
<td>Dual-energy x-ray absorption (with CT)</td>
<td>0.5-2</td>
<td>&lt;1 d/4 d</td>
</tr>
<tr>
<td>Upper GI series</td>
<td>300</td>
<td>2 yr</td>
</tr>
<tr>
<td>Small bowel series</td>
<td>250</td>
<td>20 mo</td>
</tr>
<tr>
<td>Barium enema</td>
<td>400</td>
<td>2.7 yr</td>
</tr>
<tr>
<td>CT:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>100</td>
<td>8 mo</td>
</tr>
<tr>
<td>Neck</td>
<td>150</td>
<td>1 yr</td>
</tr>
<tr>
<td>Spine</td>
<td>300</td>
<td>2 yr</td>
</tr>
<tr>
<td>Chest</td>
<td>350</td>
<td>2.3 yr</td>
</tr>
<tr>
<td>Chest (pulmonary embolism)</td>
<td>750</td>
<td>5 yr</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>100</td>
<td>5.3 yr</td>
</tr>
<tr>
<td>Abdomen</td>
<td>400</td>
<td>2.7 yr</td>
</tr>
<tr>
<td>Pelvis</td>
<td>300</td>
<td>2 yr</td>
</tr>
<tr>
<td>Radionuclide:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain (99mTc)</td>
<td>705</td>
<td>4.7 yr</td>
</tr>
<tr>
<td>Bone (18FDG)</td>
<td>315</td>
<td>2.1 yr</td>
</tr>
<tr>
<td>Thyroid (99mTc)</td>
<td>240</td>
<td>1.6 yr</td>
</tr>
<tr>
<td>Thyroid (131I)</td>
<td>95</td>
<td>8 m</td>
</tr>
<tr>
<td>Cardiac rest-stress test (99mTc)</td>
<td>470</td>
<td>3 yr</td>
</tr>
<tr>
<td>(99mTc 1-d)</td>
<td>640</td>
<td>4 yr</td>
</tr>
<tr>
<td>Lung ventilation (133Xe)</td>
<td>25</td>
<td>2 mo</td>
</tr>
<tr>
<td>Lung perfusion (133Xe)</td>
<td>100</td>
<td>8 mo</td>
</tr>
<tr>
<td>Renal (131I)</td>
<td>90-165</td>
<td>7-13 mo</td>
</tr>
<tr>
<td>Liver-spleen (131I)</td>
<td>105</td>
<td>8.4 yr</td>
</tr>
<tr>
<td>Bilary tract (131I)</td>
<td>155</td>
<td>1 yr</td>
</tr>
</tbody>
</table>

*Source: Radiology 2008;248:254-263
**Calculated using average natural background exposure in the USA (focusing radiation exposure of the population of the United States. Bethesda, MD: National Council on Radiation Protection and Measurements. 2009. NCRP No. 140)
**Magnetic Resonance Imaging**

- non-invasive technique that does not use ionizing radiation
- able to produce images in virtually any plane
- patient is placed in a magnetic field; protons (H+) align themselves along the plane of magnetization due to intrinsic polarity. A pulsed radiofrequency beam is subsequently turned on which deflected all the protons off their aligned axes due to absorption of energy from the radiofrequency beam. When the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed. This energy is measured with a detector and interpreted by a computer to generate MR images
- the MR image reflects the signal intensity picked up by the receiver. This signal intensity is dependent on:
  1. hydrogen density: tissues with low hydrogen density (e.g. cortical bone, lung) generate little to no MR signal compared to tissues with high hydrogen density (e.g. water)
  2. magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment

**Table 1. Differences Between Diffusion, T1- and T2-Weighted MR Imaging**

<table>
<thead>
<tr>
<th>Imaging Techniques</th>
<th>Contrast Enhancements</th>
<th>Main Application</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion Weighted Imaging</td>
<td>Contrast dependent on the molecular motion of water. Decreased diffusion is hypointense (dark), whereas increased diffusion is hyperintense (bright).</td>
<td>Neuroradiology</td>
<td>Sensitive for detection of acute ischemic stroke and differentiating an acute stroke from other neurologic pathologies. Acute infarction appears hypointense. Abnormal signal intensities also show restricted diffusion.</td>
</tr>
<tr>
<td>T1-Weighted</td>
<td>Fluid is hypointense (dark) and fat is hyperintense (bright)</td>
<td>Body soft tissues</td>
<td>Often considered an anatomic scan since they provide a reference for functional imaging.</td>
</tr>
<tr>
<td>T2-Weighted</td>
<td>Fluid is hyperintense (bright) and fat is hypointense (dark)</td>
<td>Body soft tissues</td>
<td>Often considered a pathologic scan since they highlight edematous areas associated with certain pathologies.</td>
</tr>
</tbody>
</table>

**Positron Emission Tomography Scans**

- non-invasive technique that involves exposure to ionizing radiation (~7 mSv)
- nuclear medicine imaging technique that produces images of functional processes in the body
- current generation models integrate PET and CT technologies into a single imaging device (PET-CT) that collects both anatomic and functional information during a single acquisition
- positron-producing radioisotope, such as 18FDG is chemically incorporated into a metabolically active molecule (e.g. glucose), injected into patient, which travels to target organ, accumulates in tissues of interest, and as radioactive substance begins to decay, gamma rays are produced which are detected by PET scanner
- contraindications: pregnancy
- advantages: shows metabolism and physiology of tissues (not only anatomic), in oncology allows diagnosis, staging, restaging, has predictive and prognostic value, can evaluate cardiac viability
- disadvantages: cost, ionizing radiation

**Table 2. Contrast Agents**

<table>
<thead>
<tr>
<th>Imaging Modality</th>
<th>Types</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray/CT</td>
<td>1. Barium (oral or rectal)</td>
<td>Radiopaque substance which helps to delineate intraluminal anatomy, may demonstrate patency, lumen integrity, or large filling defects.</td>
<td>Risk of nephrographic systemic fibrosis in patients with end-stage renal disease.</td>
<td>Previous adverse reaction to contrast; barium enema is contraindicated in toxic megacolon, acute colitis, and suspected perforation.</td>
</tr>
<tr>
<td></td>
<td>2. Iodine (IV injection)</td>
<td>Delineates intraluminal anatomy, may demonstrate patency, lumen integrity, or large filling defects; under fluoroscopy, may also give information on function of an organ.</td>
<td></td>
<td>Previous adverse reaction to contrast, renal failure, DM, pregnancy, multiple myeloma, severe heart failure and dehydration. eGFR &lt;60 may require preventative measures and follow up.</td>
</tr>
<tr>
<td>MRI</td>
<td>Gadolinium-Chelates (IV injection)</td>
<td>Shortens T1 relaxation time, thereby increasing signal intensity in T1-weighted sequences; gadodimodulin has some effect on T2-relaxation time, highlights highly vascular structures (e.g. tumors).</td>
<td>Risk of nephrographic systemic fibrosis in patients with end-stage renal disease.</td>
<td>Previous adverse reaction to contrast or if end-stage renal disease (relative contraindication).</td>
</tr>
<tr>
<td>U/S</td>
<td>Microbubbles (IV injection)</td>
<td>Since gas is highly echogenic, the microbubbles allow for echo-enhancement of a tissue.</td>
<td></td>
<td>Contraindicated in individuals with right-to-left cardiac shunts or people with known hypersensitivity reactions.</td>
</tr>
</tbody>
</table>
Chest Imaging

Chest X-Ray

Standard Views
- PA: anterior chest against film plate to minimize magnification of the heart size
- lateral: better visualization of retrocardiac space and thoracic spine (more sensitive at picking up pleural effusions)
  - helps localize lesions when combined with PA view
- AP: for bedridden patients (generally a lower quality film than PA because of enlarged cardiac silhouette)
- lateral decubitus: to assess for pleural effusion and pneumothorax in bedridden patients; however, POCUS can also be utilized for both these purposes
- lordotic: angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs

Figure 1. CXR views

Approach to CXR

Basics
- ID: patient name, MRN, sex, age
- date of exam
- markers: right and/or left
- technique: view (e.g. PA, AP, lateral), supine or erect
- indications for the study
- comparison: date of previous study for comparison (if available)
- quality of film: inspiration (6th anterior and 10th posterior ribs should be visible), penetration (thoracic spine should be visible) and rotation (clavicles vs. spinous process)

Analysis
- tubes and lines: check position and be alert for pneumothorax or pneumomediastinum
- soft tissues: neck, axillae, pectoral muscles, breasts/nipples, chest wall
  - nipple markers can help identify nipples (may mimic lung nodules)
  - amount of soft tissue, presence of masses and air (subcutaneous emphysema)
- abdomen (see Abdominal Imaging, MI10)
  - free air under the diaphragm, air-fluid levels, distention in small and large bowels
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: C-spine, thoracic spine, shoulders, ribs, sternum, clavicles
  - lytic and blastic lesions and fractures
- mediastinum: trachea, heart, great vessels
  - cardiomegaly (cardiothoracic ratio >0.5), tracheal shift, tortuous aorta, widened mediastinum
- hila: pulmonary vessels, mainstem and segmental bronchi, lymph nodes
- lungs: lung parenchyma, pleura, diaphragm
  - comment on abnormal lung opacity, pleural effusions or thickening
  - right hemidiaphragm usually higher than left due to liver
  - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm

Sodium Bicarbonate Plus N-Acetylcysteine Prophylaxis: A Meta-Analysis
J Am Coll Cardiol Intv 2009;2:1116-1124
Study: A meta-analysis of 10 RCTs.
Objective: To compare N-acetylcysteine (NAC) + sodium bicarbonate (NaHCO₃) to NAC + normal saline hydration in prevention of acute kidney injury (AKI) from IV contrast.
Patients: Those receiving IV contrast for various indications (PCI, angiography, catheterization)
Results: Combination treatment of NAC with intravenous NaHCO₃ reduced contrast-induced AKI by 35% (relative risk: 0.65; 95% confidence interval: 0.40-1.05). However, the combination of N-acetylcysteine plus NaHCO₃ did not significantly reduce renal failure requiring dialysis.
Conclusion: Combination prophylaxis should be considered for all high-risk patients (emergency cases or patients with chronic kidney disease).
Anatomy

Localizing Lesions for Parenchymal Lung Disease

- **silhouette sign**: loss of normal interfaces due to lung pathology (consolidation, atelectasis, mass), which can be used to localize disease in specific lung segments; note that pleural or mediastinal disease can also produce the silhouette sign)

- **spine sign**: on lateral films, vertebral bodies should appear progressively radiolucent as one moves down the thoracic vertebral column; if they appear more radiopaque, it is an indication of pathology (e.g. consolidation in overlying left lower lobe)

- **air bronchogram**: branching pattern of air filled bronchi on a background of fluid filled airspaces

### Table 3. Localization Using the Silhouette Sign

<table>
<thead>
<tr>
<th>Interface Lost</th>
<th>Location of Lung Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC/right superior mediastinum</td>
<td>RUL</td>
</tr>
<tr>
<td>Right heart border</td>
<td>RML</td>
</tr>
<tr>
<td>Right hemidiaphragm</td>
<td>RLL</td>
</tr>
<tr>
<td>Aortic knob/left superior mediastinum</td>
<td>LUL</td>
</tr>
<tr>
<td>Left heart border</td>
<td>Lingula</td>
</tr>
<tr>
<td>Left hemidiaphragm</td>
<td>LLL</td>
</tr>
</tbody>
</table>

**Legend**

\[\begin{array}{l}
a_1\text{ anterior 1st rib} \\
a_2\text{ anterior 2nd rib} \\
a\text{aortic arch} \\
apw\text{ aorto-pulmonary window} \\
ca\text{ carina} \\
cl\text{ clavicle} \\
cco\text{ coracoid process} \\
cpa\text{ costophrenic angle} \\
di\text{ diaphragm} \\
g\text{ gastric bubble} \\
ivc\text{ inferior vena cava} \\
l\text{ left atrium} \\
lbr\text{ left mainstem bronchus} \\
lpa\text{ left pulmonary artery} \\
lv\text{ left ventricle} \\
mf\text{ major fissure} \\
m\text{ minor fissure} \\
p3\text{ posterior 3rd rib} \\
p4\text{ posterior 4th rib} \\
pa\text{ main pulmonary artery} \\
r\text{ right atrium} \\
rbr\text{ right mainstem bronchus} \\
rpa\text{ right pulmonary artery} \\
rv\text{ right ventricle} \\
sc\text{ scapula} \\
sp\text{ spinoous process} \\
st\text{ sternum} \\
svc\text{ superior vena cava} \\
tr\text{ trachea} \\
vb\text{ vertebral body} \\
\end{array}\]

Figure 2. Location of fissures, mediastinal structures, and bony landmarks on CXR

Figure 3. Location of lobes of the lung

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## Computed Tomography Chest

### Approach to CT Chest
- **soft tissue window**
  - thyroid, chest wall, pleura
  - heart: chambers, coronary artery calcifications, pericardium
  - vessels: aorta, pulmonary artery, smaller vasculature
  - lymph nodes: mediastinal, axillary
- **bone window**
  - vertebrae, sternum, manubrium, ribs: fractures, lytic lesions, sclerosis
- **lung window**
  - trachea: patency, secretions
  - bronchial trees: anatomic variants, mucus plugs, airway collapse
  - lung parenchyma: fissures, nodules, fibrosis/interstitial changes
  - pleural space: effusions

### Types of CT Chest

<table>
<thead>
<tr>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Contrast</th>
<th>Indication</th>
</tr>
</thead>
</table>
| Standard  | Scans full lung very quickly (<1 min) | Poor at evaluating diffuse disease | ± | CXR abnormality
|           |              |          | Pleural and mediastinal abnormality |
|           |              |          | Lung cancer staging |
|           |              |          | Follow up metastases |
|           |              |          | Empyema vs. abscess |
| High Resolution | Thinner slices provide high definition of lung parenchyma | Only 5-10% lung is sampled | No | Hemoptysis |
|           |              |          | Diffuse lung disease (e.g. sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis) |
|           |              |          | Pulmonary fibrosis |
|           |              |          | Normal CXR but abnormal PFTs |
|           |              |          | Characterize solitary pulmonary nodule |
| Low Dose  | 1/5th the radiation | Decreased detail | No | Screening |
|           |              |          | Follow up infections, lung transplant, metastases |
| CTA       | Iodinated contrast highlights vasculature | Contrast can cause severe allergic reaction and is nephrotoxic | Yes | PE |
|           |              |          | Aortic aneurysms |
|           |              |          | Aortic dissection |
| CTA       | Iodinated contrast highlights vasculature | Contrast can cause severe allergic reaction and is nephrotoxic | Yes | PE |
|           |              |          | Aortic aneurysms |
|           |              |          | Aortic dissection |
| CTA       | Iodinated contrast highlights vasculature | Contrast can cause severe allergic reaction and is nephrotoxic | Yes | PE |
|           |              |          | Aortic aneurysms |
|           |              |          | Aortic dissection |

## Lung Abnormalities

### Atelectasis
- pathogenesis: collapse of alveoli due to restricted breathing, blockage of bronchi, external compression, or poor surfactant
- findings
  - increased opacity of involved segment/lobe, vascular crowding, silhouette sign, air bronchograms
  - volume loss: fissure deviation, hilar/mediastinal displacement, diaphragm elevation
  - compensatory hyperinflation of remaining normal lung
- differential diagnosis
  - obstructive (most common): air distal to obstruction is reabsorbed causing alveolar collapse
    - post-surgical, endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury) or mucous plug (cystic fibrosis)
  - compressive
    - tumor, bulla, effusion, enlarged heart, lymphadenopathy
  - traction (cicatrization): due to scarring, which distorts alveoli and contracts the lung
  - adhesive: due to lack of surfactant
    - hyaline membrane disease, prematurity
  - passive (relaxation): a result of air or fluid in the pleural space
    - pleural effusion, pneumothorax
- management: in the absence of a known etiology, persisting atelectasis must be investigated (i.e. CT thorax) to rule out a bronchogenic carcinoma

### Consolidation
- pathogenesis: fluid (water, blood), inflammatory exudates, protein, or tumor in alveoli
- findings
  - air bronchograms: lucent branching bronchi visible through opacification
  - airspace nodules: fluffy, patchy, poorly defined margins with later tendency to coalesce, may take on lobar or segmental distribution
  - silhouette sign
• differential diagnosis
  † fluid: pulmonary edema, blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
  † inflammatory: bacterial infections, TB, allergic hypersensitivity alveolitis, BOOP, allergic bronchopulmonary aspergillosis, aspiration, sarcoidosis
  † protein: pulmonary alveolar proteinosis
  † tumor: bronchoalveolar carcinoma, lymphoma
• management: varies depending on the pattern of consolidation, which can suggest different etiologies; should also be done in the context of clinical picture

Interstitial Disease
• pathogenesis: pathological process involving the interlobular connective tissue (i.e., “scaffolding of the lung”)
• findings
  † linear: fine lines caused by thickened connective tissue septae
    † Kerley A: long thin lines in upper lobes
    † Kerley B: short horizontal lines extending from lateral lung margin
    † Kerley C: diffuse linear pattern throughout lung
  † nodular: 1-5 mm well-defined nodules distributed evenly throughout lung
    † seen in malignancy, pneumoconiosis and granulomatous disease (e.g., sarcoidosis, miliary TB)
  † reticular (honeycomb): parenchyma replaced by thin-walled cysts suggesting extensive destruction of pulmonary tissue and fibrosis
    † seen in IPF, asbestosis, and CVD
    † watch for pneumothorax as a complication
  † reticulonodular: combination of reticular and nodular patterns
  † may also see signs of airspace disease (atelectasis, consolidation)
• differential diagnosis
  † occupational/environmental exposure
    † inorganic: asbestosis, coal miner’s pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
    † organic: hypersensitivity pneumonitis, bird fancier’s lung, farmer’s lung (moldy hay), and other organic dust
  † autoimmune: CVD (e.g., rheumatoid arthritis, scleroderma, SLE, polymyositis, mixed connective tissue disease), IBD, celiac disease, vasculitis
  † drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, phenytoin, carbamazepine, fluoxetine, amiodarone, chemotherapy (e.g., methotrexate), heroin, cocaine, methadone
  † infections: non-tuberculous mycobacteria, certain fungal infections
  † idiopathic: hypersensitivity pneumonitis, IPF, BOOP
  † for Causes of Interstitial Lung Disease Classified by Distribution, see Respirology, R13
• management: high resolution CT thorax and biopsy

Pulmonary Nodule
• findings: round opacity ± silhouette sign
  † note: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers
• differential diagnosis
  † extrapulmonary density: nipple, skin lesion, electrode, pleural mass, bony lesion
  † solitary nodule
    † tumor: carcinoma, hamartoma, metastasis, bronchial adenoma
    † inflammation: histoplasmosis, tuberculosis, coccidioidomycosis
    † vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
  † multiple nodules: metastases, abscess, granulomatous lung disease (TB, fungal, sarcoid, rheumatoid nodules, silicosis, GPA)
• management: clinical information and CT appearance determine level of suspicion of malignancy
  † if high probability of malignancy, invasive testing (fine needle aspiration, transbronchial/ transthoracic biopsy) is indicated
  † if low probability of malignancy, repeat CXR or CT in 1-3 mo and then every 6 mo for 2 yr; if no change, then >99% chance benign
Table 5. Characteristics of Benign and Malignant Pulmonary Nodules

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin</td>
<td>Ill-defined/spiculated (“corona radiata”)</td>
<td>Well-defined</td>
</tr>
<tr>
<td>Contour</td>
<td>Lobulated</td>
<td>Smooth</td>
</tr>
<tr>
<td>Calcification</td>
<td>Eccentric or stippled</td>
<td>Diffuse, central, popcorn, concentric</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>20-460 d</td>
<td>&lt;20 d or &gt;460 d</td>
</tr>
<tr>
<td>Other Features</td>
<td>Cavititation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>&gt;3 cm</td>
<td>&lt;3 cm</td>
</tr>
<tr>
<td>Cavititation</td>
<td>Yes, especially with wall thickness &gt;15 mm, eccentric cavity and shaggy internal margins</td>
<td>No</td>
</tr>
<tr>
<td>Satellite Lesions</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Pulmonary Vascular Abnormalities

Pulmonary Edema

- **Pathogenesis:** fluid accumulation in the airspaces of the lungs
- **Findings**
  - Vascular redistribution/enlargement, cephalization, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
  - Fluid initially collects in interstitium
    - Loss of definition of pulmonary vasculature
    - Peribronchial cuffing
    - Kerley B lines
    - Reticulonodular pattern
    - Thickening of interlobar fissures
    - As pulmonary edema progresses, fluid begins to collect in alveoli causing diffuse air space disease often in a “bat wing” or “butterfly” pattern in perihilar regions with tendency to spare the outermost lung fields
- **Differential diagnosis:** cardiogenic (e.g. CHF), renal failure, volume overload, non-cardiogenic (e.g. ARDS)

Pulmonary Embolism

- **Pathogenesis:** arterial blockage in the lungs due to emboli from pelvic or leg veins, rarely from PICC lines, ports, or air, fat, or amniotic fluid (difficult to diagnose on imaging except by combination of clinical history and CXR and CT findings of ARDS)
- **Findings**
  - **CXR:** Westermark sign (localized pulmonary oligemia), Hampton’s hump (triangular peripheral infarct), enlarged right ventricle and right atrium, atelectasis, pleural effusion, and rarely pulmonary edema
  - **Definitive imaging study:** CT pulmonary angiography to look for filling defect in contrast-filled pulmonary arteries (emboli can be seen up to 4th order arterial branching)
  - V/Q scan: not a diagnostic study

Pleural Abnormalities

Pleural Effusion

<table>
<thead>
<tr>
<th>X-Ray Projection</th>
<th>Minimum Volume to Visualize</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral decubitus</td>
<td>25 mL: most sensitive</td>
<td></td>
</tr>
<tr>
<td>Upright lateral</td>
<td>50 mL: meniscus seen in the posterior costophrenic sulcus</td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>200 mL</td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>Diffuse haziness</td>
<td></td>
</tr>
</tbody>
</table>

- A horizontal fluid level is seen only in a hydropneumothorax (i.e. both fluid and air within pleural cavity)
- Effusion may exert mass effect, shift trachea and mediastinum to opposite side, or cause atelectasis of adjacent lung
- U/S is superior to plain film for detection of small effusions and may also aid in thoracentesis, and POCUS is now standard of care in acute situations
- Fluid level >1 cm on lateral decubitus film is indication to perform thoracentesis

Pneumothorax

- **Pathogenesis:** gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
• findings
  ▪ upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air
  ▪ more obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiorly)
  ▪ more difficult to detect on supine film; look for the "deep (costophrenic) sulcus" sign, "double diaphragm" sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  ▪ mediastinal shift may occur if tension pneumothorax
  ▪ differential diagnosis: spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, CVP line insertion), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung
  ▪ management: needle decompression or chest tube insertion, repeat CXR to ensure resolution

Asbestos
• asbestos exposure may cause various pleural abnormalities including benign plaques (most common) that may calcify, diffuse pleural fibrosis, effusion, and malignant mesothelioma

Mediastinal Abnormalities

Mediastinal Mass
• the mediastinum is divided into four compartments; this provides an approach to the differential diagnosis of a mediastinal mass
• anterior (anterior border formed by the sternum and posterior border by the heart and great vessels)
  ▪ 4 Ts: see sidebar
    ▪ cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
• middle (extending behind anterior mediastinum to a line 1 cm posterior to the anterior border of the thoracic vertebral bodies)
  ▪ esophageal carcinoma, esophageal duplication cyst, metastatic disease, lymphadenopathy (all causes), hiatus hernia, bronchogenic cyst
• posterior (posterior to the middle line described above)
  ▪ neurogenic tumor (e.g. neurofibroma, schwannoma), multiple myeloma, pheochromocytoma, neuromenteric cyst, thoracic duct cyst, lateral meningocele, Bochdalek hernia, extramedullary hematopoiesis
• superior boundaries (superiorly by thoracic inlet, inferiorly by plane of the sternal angle, anteriorly by manubrium, posteriorly by T1-T4, laterally by pleura)
• in addition, any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, and hematoma

Enlarged Cardiac Silhouette
• heart borders
  ▪ on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
  ▪ on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle
• cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
• using a good quality erect PA chest film in adults, cardiothoracic ratio of >0.5 is abnormal
• differential of ratio >0.5
  ▪ cardiomegaly (myocardial dilatation or hypertrophy)
  ▪ pericardial effusion
  ▪ poor inspiratory effort/low lung volumes
  ▪ pectus excavatum
• ratio <0.5 does not exclude enlargement (e.g. cardiomegaly + concomitant hyperinflation)
• pericardial effusion: globular heart with loss of indentations on left mediastinal border
• RA enlargement: increase in curvature of right heart border and enlargement of SVC
• LA enlargement: straightening of left heart border; increased opacity of lower right side of cardiovascular shadow (double heart border); elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film), distance between left main bronchus and “double” heart border >7 cm, splayed carina (late sign)
• RV enlargement: elevation of cardiac apex from diaphragm; anterior enlargement leading to loss of retrosternal air space on lateral; increased contact of right ventricle against sternum
• LV enlargement: displacement of cardiac apex inferiorly and posteriorly – “boot-shaped” heart

DDx Anterior Mediastinal Mass
4 Ts
- Thyroid
- Thymic neoplasm
- Teratoma
- Terrible lymphoma

Mediastinal Masses
Approximately 60% of anterior, 30% of middle, and 15% of posterior mediastinal masses are malignant

Elevated Hemidiaphragm Suggests:
- PAL DIP
- Pregnancy
- Atelectasis
- Lung resection
- Diaphragmatic paralysis
- Intra-abdominal process
- Pneumomediastinum
- Pleural effusion also may result in apparent elevation

Depressed Hemidiaphragm Suggests
- TALC
- Tumor
- Asthma
- Large pleural effusion
- COPD

Figure 14. Lateral CXR showing 4 mediastinal compartments
Tubes, Lines, and Catheters

- ensure appropriate placement and assess potential complications of lines and tubes
- avoid mistaking a line/tube for pathology (e.g. oxygen rebreather mask for pneumothoraces)

Central Venous Catheter

- used for fluid and medication administration, vascular access for hemodialysis, and CVP monitoring
- tip must be located proximal to right atrium to prevent inducing arrhythmias or perforating wall of atrium
  - if monitoring CVP, catheter tip must be proximal to venous valves
- tip of well positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle, and inferiorly by top of RA
- course should parallel course of SVC – if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

Endotracheal Tube

- frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- tip should be located 4 cm above tracheal carina – avoids bronchus intubation and vocal cord irritation
- maximum inflation diameter <3 cm to avoid necrosis of tracheal mucosa and rupture – ensure diameter of balloon is less than tracheal diameter above and below balloon
- complications: aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

Nasogastric Tube

- tip and sideport should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- complications: aspiration (parenchymal opacities), intracranial perforation (trauma patients), pneumothorax

Swan-Ganz Catheter

- to monitor pulmonary capillary wedge pressure and to measure cardiac output for suspected LV dysfunction
- tip should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- if tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture
- complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

Chest Tube

- in dorsal and caudal portion of pleural space to evacuate fluid
- in ventral and cephalad portions of pleural space to evacuate pneumothoraces
- tube may lie in fissure as long as functioning
- complications: lung perforation (mediastinal opacities)

Abdominal Imaging

Abdominal X-Ray

- indications
  - acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction, large bowel obstruction
  - chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
  - not useful in: GI bleeds, chronic anemia, vague GI symptoms
- AXR 3 most common views: left lateral decubitus, supine, erect upright (see Figure 16, MI12)
Anatomy

- abdomen divided into 2 cavities
  - peritoneal cavity: lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
  - retroperitoneal cavity: contains several organs situated posterior to the peritoneal cavity; the contour of these can often be seen on radiographs

Table 7. Differentiating Small and Large Bowel

<table>
<thead>
<tr>
<th>Property</th>
<th>Small Bowel</th>
<th>Large Bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal Folds</td>
<td>Uninterrupted valvulae conniventes</td>
<td>Interrupted haustra extend only</td>
</tr>
<tr>
<td></td>
<td>(or plicae circularis)</td>
<td>partway across lumen</td>
</tr>
<tr>
<td>Location</td>
<td>Central</td>
<td>Peripheral (picture frame)</td>
</tr>
<tr>
<td>Maximum Diameter</td>
<td>3 cm</td>
<td>6 cm (9 cm at cecum)</td>
</tr>
<tr>
<td>Maximum Fold Thickness</td>
<td>3 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Other</td>
<td>Rarely contains solid fecal material</td>
<td>Commonly contains solid fecal</td>
</tr>
</tbody>
</table>

Approach to Abdominal X-Ray

- mnemonic: “Free ABDO”
- Free = free air and fluid
  - free fluid
    - small amounts of fluid: increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
    - large amounts of fluid: diffuse increased opacification on supine film; bowel floats to center of anterior abdominal wall
    - ascites and blood (hemoperitoneum) are the same density on the radiograph and therefore cannot be differentiated
    - free intraperitoneal air suggests rupture of a hollow viscus (anterior duodenum, transverse colon), penetrating trauma, or recent (<7 d) surgery
  - A = air in the bowel (can be normal, ileus, or obstruction)
    - volvulus – twisting of the bowel upon itself; from most to least common:
      - sigmoid: “coffee bean” sign (massively dilated sigmoid projects to right or mid-upper abdomen) with proximal dilation
      - cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
      - gastric: rare
      - transverse colon: rare (usually young individuals)
      - small bowel: “corkscrew sign” (rarely diagnosed on plain films, seen best on CT)
    - toxic megacolon
      - manifestation of fulminant colitis
      - extreme dilatation of colon (>6.5 cm) with mucosal changes (e.g. foci of edema, ulceration, pseudopolyps), loss of normal haustral pattern
  - B = bowel wall thickening
    - increased soft tissue density in bowel wall, thumb-like indentations in bowel wall (“thumb-printing”), or a picket-fence appearance of the valvulae conniventes (“stacked coin” appearance)
    - may be seen in IBD, infection, ischemia, hypoproteinemic states, and submucosal hemorrhage
  - D = densities
    - bones: look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
    - abnormal calcifications: approach by location
      - RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
      - RLQ: ureteral stone, appendicolith, gallstone ileus
      - LUQ: renal stone, adrenal calcification, tail of pancreas
      - LLQ: ureteral stone
      - central: aorta/aortic aneurysm, pancreas, lymph nodes
      - pelvis: phleboliths (i.e. calcified veins), uterine fibroids, bladder stones
  - O = organs
    - kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
    - outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)
Figure 16. Normal AXRs: (left) supine anteroposterior AXR, (middle) upright anteroposterior AXR, and (right) left lateral decubitus AXR

Table 8. Abnormal Air on Abdominal X-Ray

<table>
<thead>
<tr>
<th>Air</th>
<th>Appearance</th>
<th>Common Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraluminal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Upright film: air under diaphragm</td>
<td>Perforated viscus Post-operative (up to 10 d to be resorbed)</td>
</tr>
<tr>
<td>(pneumoperitoneum)</td>
<td>Left lateral decubitus film: air between liver and abdominal wall</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supine film: gas outlines of structures not normally seen:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Inner and outer bowel wall (Rigler’s sign)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Falciform ligament</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pentoneal cavity (“football” sign)</td>
<td></td>
</tr>
<tr>
<td>Retropertoneal</td>
<td>Gas outlining retropertoneal structures allowing increased visualization:</td>
<td>Perforation of retropertoneal segments of bowel: duodenal ulcer, post-colonoscopy</td>
</tr>
<tr>
<td></td>
<td>• Psoas shadows</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Renal shadows</td>
<td></td>
</tr>
<tr>
<td>Intramural</td>
<td>Lucent air streaks in bowel wall, 2 types:</td>
<td></td>
</tr>
<tr>
<td>(pneumatosis intestinalis)</td>
<td>1. Linear</td>
<td>1. Linear: ischemia, necrotizing enterocolitis</td>
</tr>
<tr>
<td></td>
<td>2. Rounded (cystoides type)</td>
<td>2. Rounded/cystoides (generally benign): primary (idiopathic), secondary to COPD</td>
</tr>
<tr>
<td>Intraluminal</td>
<td>Dilated loops of bowel, air-fluid levels</td>
<td>Adynamic (paralytic) ileus, mechanical bowel obstruction</td>
</tr>
<tr>
<td>Loculated</td>
<td>Mottled, localized in abnormal position without normal bowel features</td>
<td>Absscess (evaluate with CT)</td>
</tr>
<tr>
<td>Biliary</td>
<td>Air centrally over liver</td>
<td>Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis</td>
</tr>
<tr>
<td>Portal Venous</td>
<td>Air peripherally over liver in branching pattern</td>
<td>Bowel ischemia/infarction</td>
</tr>
</tbody>
</table>

Table 9. Adynamic Ileus vs. Mechanical Obstruction

<table>
<thead>
<tr>
<th>Feature</th>
<th>Adynamic Ileus</th>
<th>Mechanical Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibre of Bowel Loops</td>
<td>Normal or dilated</td>
<td>Usually dilated</td>
</tr>
<tr>
<td>Air-Fluid Levels (erect and left lateral decubitus films only)</td>
<td>Same level in the same single loop</td>
<td>Multiple air fluid levels giving “step ladder” appearance, dynamic (indicating peristalsis present), “string of pearls” (row of small gas accumulations in the dilated valvulae conniventes)</td>
</tr>
<tr>
<td>Distribution of Bowel Gas</td>
<td>Air throughout GI tract is generalized or localized</td>
<td>Dilated bowel up to the point of obstruction (i.e. transition point)</td>
</tr>
<tr>
<td></td>
<td>• In a localized ileus (e.g. pancreatitis, appendicitis), dilated “sentinel loop” remains in the same location on serial films, usually adjacent to the area of inflammation</td>
<td>No air distal to obstructed segment</td>
</tr>
<tr>
<td></td>
<td>&quot;Hairpin” (180°) turns in bowel</td>
<td>“Hairpin” (180°) turns in bowel</td>
</tr>
</tbody>
</table>

Abdominal CT
- indications for plain CT: renal colic, hemorrhage
- indications for CT with contrast
  - IV contrast given immediately before or during CT to allow identification of arteries and veins
  - portal venous phase: indicated for majority of cases
  - biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumors
  - oral contrast: barium or water soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
  - rectal contrast: given for investigation of colonic lesions
  - caution: contrast allergy (may premedicate with steroids and antihistamine)
  - contraindication: impaired renal function, based on eGFR

Biliary vs. Portal Venous Air
“Go with the flow”: air follows the flow of bile or portal venous blood
- Biliary air is most prominent centrally over the liver
- Portal venous air is most prominent peripherally

ICV Function in Large Bowel Obstruction
- Competent ICV: Distention of large bowel between obstruction and ICV; small bowel unaffected
  - Higher risk of perforation, especially with cecal distention >10 cm
- Incompetent ICV: Distention of large and small bowel
Approach to Abdominal Computed Tomography

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ/structure individually, from top to bottom evaluating size and shape of each area of increased or decreased density
- evaluate the following
  - soft tissue window
    - liver, gallbladder, spleen, and pancreas
    - adrenals, kidneys, ureters, and bladder
    - stomach, duodenum, small bowel mesentery, and colon/appendix
    - retroperitoneum: aorta, vena cava, and mesenteric vessels; look for adenopathy in vicinity of vessels
    - peritoneal cavity for fluid or masses
    - abdominal wall and adjacent soft tissue
  - lung window
    - visible lung (bases)
  - bone window
    - vertebrae, spinal cord, and bony pelvis

CT and Bowel Obstruction
- cause of bowel obstruction rarely found on plain films – CT is best choice for imaging
- the “3,6,9” rule is a very useful guide to determining when the bowel is dilated; the maximum diameter of the bowel is 3 cm for small bowel, 6 cm for large bowel, and 9 cm for cecum; this can also be useful to distinguish small and large bowel, and to assess for ‘impending’ cecal perforation (e.g. post-untreated Ogilvie's syndrome)
- closed-loop obstruction: an obstruction in two locations (usually small bowel) creating a loop of bowel segment obstructed both proximally and distally; complications (e.g. ischemia, perforation, necrosis) may occur quickly

CT Colonography (virtual colonoscopy)
- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumors)
- two CT scans of the abdomen (prone and supine) after the instillation of carbon dioxide into a prepped colon
- computer reconstruction of 2D CT images into a 3D intraluminal view of the colon in order to look for masses
- lesions seen on 3D images correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, staging of obstructing colonic lesions

Contrast Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ</th>
<th>Procedure Description</th>
<th>Assessment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine Esophagogram</td>
<td>Cervical esophagus</td>
<td>Contrast agent swallowed Recorded for later playback and analysis</td>
<td>Dysphagia, swallowing incoordination, recurrent aspiration, post-operative cleft palate repair</td>
<td>Aspiration, webs (partial occlusion), Zenker’s diverticulum, criopharyngeal bar, laryngeal tumor</td>
</tr>
<tr>
<td>Barium Swallow</td>
<td>Thoracic esophagus</td>
<td>Contrast agent swallowed under fluoroscopy, selective images captured</td>
<td>Dysphagia, rule out GERD, post esophageal surgery</td>
<td>Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear</td>
</tr>
<tr>
<td>Upper GI Series</td>
<td>Thoracic esophagus, stomach, or duodenum</td>
<td>Double contrast study: 1. Barium to coat mucosa, then 2. Gas pills for distention Patient NPO after midnight</td>
<td>Dyspepsia, investigate possible upper GI bleed, weight loss/anemia, post gastric surgery</td>
<td>Ulcers, neoplasms, filling defects</td>
</tr>
<tr>
<td>Barium Enema</td>
<td>Large bowel</td>
<td>Colon filled retrograde with barium and air or CO2 Bowel prep the night before procedure</td>
<td>Altered bowel habits, suspected lower GI bleed, weight loss/anemia, rule out large bowel obstruction, suspected perforation, check surgical anastomosis, history of polyps</td>
<td>Diverticulosis, neoplasms, IBD, intussusception (can be reduced with barium or air enema), volvulus</td>
</tr>
<tr>
<td>Small Bowel Follow Thru</td>
<td>Entire small bowel</td>
<td>Single contrast images following upper GI series</td>
<td>GI bleed with nondiagnostic upper GI series/barium enema, weight</td>
<td>Neoplasms, IBD, malabsorption, infection</td>
</tr>
<tr>
<td>Small Bowel Enema</td>
<td>Entire small bowel</td>
<td>Duodenal intubation: 1. Barium/methyl cellulose infusion and fluoroscopic evaluation 2. CT enteroclysis with water infusion</td>
<td>IBD, malabsorption, weight loss/anemia, Meckel’s diverticulum</td>
<td>Neoplasms, IBD, malabsorption, infection</td>
</tr>
</tbody>
</table>
Specific Visceral Organ Imaging

Liver
- U/S: assessment of cysts, abscesses, tumors, biliary tree
- CT ± IV: most popular procedure for imaging the liver parenchyma (primary liver tumors, metastases, cysts, abscesses, trauma, cirrhosis)
- MR: also excellent in evaluation of primary liver tumors, liver metastases, and other parenchymal conditions, and is particularly helpful in differentiating common benign hepatic hemangiomas from primary liver tumors and metastases
- findings
  - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
  - portal HTN: increased portal vein diameter, collateral veins, splenomegaly (≥12 cm), portal vein thrombosis, recanalization of the umbilical vein
  - porto-systemic shunts: caput medusa, esophageal varices, spontaneous spleno-renal shunt
  - U/S: cirrhosis appears nodular and hypechoic with irregular areas of atrophy of the right lobe and hypertrophy of the caudate or left lobes
  - CT: fatty infiltration appears hypodense
  - in order to be visualized, some masses require contrast

<p>| Table 11. Triphasic/Quadriphasic Liver Protocol |</p>
<table>
<thead>
<tr>
<th>Phase</th>
<th>Time Frame</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Contrast CT</td>
<td>0</td>
<td>For all initial investigations of liver lesions</td>
</tr>
<tr>
<td>Arterial Phase</td>
<td>20-30 s</td>
<td>Early and late arterial phase on multidetector CT</td>
</tr>
<tr>
<td>Portal Venous Phase</td>
<td>60-70 s</td>
<td>Provides maximum enhancement of hepatic tissue</td>
</tr>
<tr>
<td>Equilibrium (Delayed) Phase</td>
<td>120-180 s</td>
<td>Hemangioma: persistent enhancement suggests blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement of fibrous/scar tissue (HCC capsule, focal nodular hyperplasia, cholangiocarcinoma)</td>
</tr>
</tbody>
</table>

<p>| Table 12. Imaging of Liver Masses |</p>
<table>
<thead>
<tr>
<th>Mass</th>
<th>U/S</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>Multiple masses of variable echotexture</td>
<td>Usually low attenuation on contrast enhanced scan</td>
</tr>
<tr>
<td>HCC</td>
<td>Single/multiple masses, or diffuse infiltration</td>
<td>Hypervascular enhances in arterial and washes out in venous phase with portal venous tumor thrombus</td>
</tr>
<tr>
<td>Abscess</td>
<td>Poorly defined, irregular margin, hypoechoic contents</td>
<td>Low-attenuation lesion with an irregular enhancing wall</td>
</tr>
<tr>
<td>Hydatid Cyst</td>
<td>Simple/multiloculated cyst</td>
<td>Low-attenuation simple or multiloculated cyst; calcification</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Homogeneous hypechoic mass</td>
<td>Peripheral globular enhancement in arterial phase scans; central-filling and persistent enhancement on delayed scans</td>
</tr>
<tr>
<td>Focal Nodular Hyperplasia</td>
<td>Well-defined mass, central scar seen in 50%</td>
<td>Hypervascular mass in arterial phase and isoattenuation to liver in portal venous phase</td>
</tr>
<tr>
<td>Hepatic Adenoma</td>
<td>Most common in young women taking oral contraceptives. Well-defined mass with hypechoic areas due to hemorrhage</td>
<td>Well-defined hypervascular lesion with enlarged central vessel becoming slightly isoattenuating in venous phase</td>
</tr>
</tbody>
</table>

Spleen
- U/S, CT, nuclear medicine scan (nuclear medicine only to distinguish ectopic splenic tissue from enhancing tumors)
- CT for splenic trauma (hemorrhage)

Biliary Tree
- U/S: bile ducts usually visualized only if dilated, secondary to obstruction (e.g. choledocholithiasis, benign stricture, mass)
- CT: dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- MRC, ERCP, PTC: further evaluation of obstruction and possible intervention

Figure 18. ERCP: biliary tree

Liver Mass DDx
- 5 Hs
- HCC
- Hydatid cyst
- Hemangioma
- Hepatic adenoma
- Hyperplasia (focal nodular)

Revised Estimates of Diagnostic Test Sensitivity and Specificity in Suspected Biliary Tract Disease
Arch Intern Med 1998; 158:2573-2581

Purpose: To assess the sensitivity and specificity of tests used to diagnose choledolithiasis and acute cholecystitis, including ultrasonography, oral cholecystography, radionucleotide scanning with Technetium, MRI, CT.

Study Characteristics: Meta-analysis of 30 studies evaluating the use of different imaging modalities in the diagnosis of biliary tract disease.

Participants: No limits.

Main Outcomes: Sensitivity and specificity of the different imaging modalities, using the gold standard of surgery, autopsy, or 3 mo clinical follow-up for cholecystitis. For acute cholecystitis, pathologic findings, confirmation of an alternate disease, or clinical resolution during hospitalization for cholecystitis were used as the standard.

Results: For evaluating choledolithiasis, US had the best unadjusted sensitivity (0.97; 95% CI 0.95-0.99) and specificity (0.99; 95% CI 0.98-1.00) and adjusted (for verification bias) sensitivity (0.94; 95% CI 0.76-1.00) and specificity (0.99; 95% CI 0.98-1.00). For evaluating acute cholecystitis, radionucleotide scanning has the best sensitivity (0.97; 95% CI 0.86-0.98) and specificity (0.92; 95% CI 0.86-0.95).

Conclusions: U/S is the test of choice for diagnosing choledolithiasis and radionucleotide scanning is the superior test for diagnosing acute cholecystitis.
Pancreas
- tumors
  - U/S: mass is more echogenic than normal pancreatic tissue
  - CT: preferred modality for diagnosis/staging
- ductal dilatation secondary to stone/tumor
- MRCP: imaging of ductal system using MRI cholangiography; no therapeutic potential
- ERCP: endoscope to inject dye into the biliary tree and x-ray imaging to assess pancreatic and biliary ducts; therapeutic potential (sten placement, stone retrieval); acute pancreatitis is a complication in 5% of diagnostic procedures and 10% of therapeutic procedures

“itis” Imaging

Acute Cholecystitis
- pathogenesis: inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or, in the case of acalculous cholecystitis, due to gallbladder ischemia or cholestasis (see General Surgery, GS46)
- best imaging modality: U/S (best sensitivity and specificity); nuclear medicine (HIDA scan) can help diagnose cases of acalculous or chronic cholecystitis
- findings: thick wall, pericholecystic fluid, gallbladder, positive sonographic Murphy's sign
- management: cholecystectomy

Acute Appendicitis
- pathogenesis: luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess or peritonitis (see General Surgery, GS28)
- best imaging modality: U/S or CT
- findings
  - U/S: thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible; may also demonstrate other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
  - CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage
- management: appendectomy

Acute Diverticulitis
- pathogenesis: erosion of the intestinal wall (most commonly rectosigmoid) by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro- or macroscopic perforation (see General Surgery, GS31)
- best imaging modality: CT is modality of choice, although U/S is sometimes used
- contrast: oral and rectal contrast given before CT to opacify bowel
- findings
  - cardinal signs: thickened wall, mesenteric infiltration, abscess
  - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
  - sometimes difficult to distinguish from perforated cancer (therefore send abscess fluid for cytology and follow up with colonoscopy)
  - if chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)
- management: ranges from antibiotic treatment to surgical intervention; can use imaging to follow progression

Acute Pancreatitis
- pathogenesis: activation of proteolytic enzymes within pancreatic cells leading to local and systemic inflammatory response (see Gastroenterology, G50); a clinical/biochemical diagnosis
- best imaging modality: imaging used to support diagnosis and evaluate for complications (diagnosis cannot be excluded by imaging alone)
  - U/S good for screening and follow-up
  - CT is useful in advanced stages and in assessing for complications (1st line imaging test)
- findings
  - U/S: hypoechoic enlarged pancreas (if ileus present, gas obscures pancreas)
  - CT: enlarged pancreas, edema, stranding changes in surrounding fat with indistinct fat planes, mesenteric and Gerota's fascia thickening, pseudocyst in lesser sac, abscess (gas or thick-walled fluid collection), pancreatic necrosis (low attenuation gas-containing non-enhancing pancreatic tissue), hemorrhage
- management: supportive therapy
  - CT-guided needle aspiration and/or drainage done for abscess when clinically indicated
  - pseudocyst may be followed by CT and drained if symptomatic

Angiography requires active blood loss 1-1.5 mL/min under optimal conditions for a bleeding site to be visualized in cases of lower GI bleeding
Chronic Pancreatitis
- pathogenesis: (see Gastroenterology, G51)
- best imaging modality: MRCP (can show calcification and duct obstruction)
- findings: U/S, CT scan, and MRI may show calcifications, ductal dilatation, enlargement of the pancreas and fluid collections (e.g. pseudocysts) adjacent to the gland

**Angiography of GI Tract**
- anatomy of the GI tract arterial blood supply branches
  - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
  - superior mesenteric artery: jejunal, ileal, ileo-colic, right colic, middle colic
  - inferior mesenteric artery: left colic, superior rectal
- imaging modalities
  - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
    - flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
  - CT angiogram: modality of choice, non-invasive using IV contrast (no catheterization required)

**Genitourinary System and Adrenal**

**Urological Imaging**

KUB
- a frontal supine radiograph of the abdomen
- indication: useful in evaluation of radio-opaque renal stones (all stones but uric acid and indinavir), as well as indwelling ureteric stents or catheters
- findings: addition of IV contrast excreted by the kidney (intravenous urogram) allows greater visualization of the urinary tract, but has been largely replaced by CT urography

**Abdominal CT**

**Renal Masses**
- Bozniak classification for cystic renal masses
  - class I-II: benign and can be disregarded
  - class IIF: should be followed
  - class III-IV: suspicious for malignancy, requiring additional workup

<table>
<thead>
<tr>
<th>Classes</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Renal Cysts</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>Fluid-attenuating well-defined lesion, no septation, no calcification, no solid components, hair thin wall</td>
</tr>
<tr>
<td>Class II</td>
<td>Same as class I + fine calcification or moderately thickened calcification in septae or walls; also includes hyperdense cysts (&lt;3 cm) that do not enhance with contrast</td>
</tr>
<tr>
<td>Complex Renal Cysts</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>Thick irregular walls ± calcifications ± septated, enhancing walls or septa with contrast</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>Same as class III + soft tissue enhancement with contrast (defined as &gt;10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase ± areas of necrosis</td>
</tr>
</tbody>
</table>

- plain CT KUB
  - indications: general imaging of renal anatomy, renal colic symptoms, assessment of renal calculi (size and location), and hydronephrosis prior to urological treatment
- CT urography
  - indications: investigation of cause of microscopic/gross hematuria, detailed assessment of urinary tracts (excretory phase), high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts, assessment of renal calculi
  - phases: unenhanced, excretory
- renal triphasic CT
  - indications: standard imaging for renal masses, allows accurate assessment of renal arteries and veins, better characterization of suspicious renal masses, especially in differentiating renal cell carcinoma from more benign masses, and pre-operative staging
  - phases: unenhanced, arterial and venous (nephrographic)

**Imaging Modality Based on Presentation**
- Acute testicular pain = Doppler, U/S
- Amenorrhea = U/S, MRI (brain)
- Bloating = U/S, CT
- Flank pain = U/S, CT
- Hematuria = U/S, Cystoscopy, CT
- Infertility = HSG, MRI
- Lower abdominal mass = U/S, CT
- Lower abdominal pain = U/S, CT
- Renal colic = U/S, KUB, CT
- Testicular mass = CT
- Urethral stricture = Urethrogram

**Figure 21. Triphasic CT of an angiomyolipoma:** showing fat density with non-contrast scan, mildly enhancing with contrast

**Figure 22. Triphasic CT of a renal cell carcinoma:** showing arterial enhancing right renal lesion with venous washout (shunting)
Ultrasound
- indications: initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic renal masses vs. complicated cysts); technique of choice for screening patients with suspected hydronephrosis (no IV contrast injection, no radiation to patient, and can be used in patients with renal failure); TRUS useful to evaluate prostate gland and guide biopsies; Doppler U/S to assess renal vasculature
- findings: solid renal masses are echogenic (bright on U/S), cystic renal masses have smooth well-defined walls with anechoic interior (dark on U/S), and complicated cysts have internal echoes within a thickened, irregular wall

Retrograde Pyelography
- indications: visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium, ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction)
- findings: only yields information about the collecting systems (renal pelvis and associated structures), no information regarding the parenchyma of the kidney

Voiding Cystourethrogram
- bladder filled with contrast to the point where voiding is triggered
- fluoroscopy (continuous, real-time) to visualize bladder
- indications: children with recurrent UTIs, hydronephrosis, hydroureter, suspected lower urinary tract obstruction or vesicoureteral reflex
- findings: contractility and evidence of vesicoureteric reflex

Retrograde Urethrogram
- a small Foley catheter placed into penile urethral opening
- indications: used mainly to study strictures or trauma to the male urethra; first-line study if trauma with blood present at urethral meatus

MRI
- advantages: high spatial and tissue resolution, lack of exposure to ionizing radiation and nephrotoxic contrast agents
- indications: indicated over CT for depiction of renal masses in patients with previous nephron sparing surgery, patients requiring serial follow-up (less radiation dosage), patients with reduced renal function, and patients with solitary kidneys

Renal Nuclear Scan

Table 14. Renal Scan Tests

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Uses</th>
<th>Radionuclide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renogram</td>
<td>To assess renal function and collecting system: evaluation of renal failure, workup of urinary tract obstruction and HTN, investigation of renal transplant</td>
<td>$^{99m}$Tc-mercaptoacetyltriglycine (MDP), $^{99m}$Tc-DTPA, or $^{99m}$Tc-macroaggregated albumin (MAA)</td>
</tr>
<tr>
<td>Morphological</td>
<td>Assess renal anatomy: investigation of pyelonephritis and cortical scars</td>
<td>$^{99m}$Tc-DMSA, $^{99m}$Tc-glucoheptonate</td>
</tr>
</tbody>
</table>

Gynecological Imaging

Ultrasound
- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air containing loops of bowel
  - indication: good initial investigation for suspected pelvic pathology
  - TVUS provides enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves at reduced distances
  - indication: improved assessment of ovaries, first trimester development, and ectopic pregnancies

Hysterosalpingogram
- indications: useful for assessing pathology of the uterine cavity and fallopian tubes, evaluating uterine abnormalities (e.g. bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)
- performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent

CT/MRI
- indications: evaluating pelvic structures, especially those adjacent to the adnexa and uterus
- invaluable for staging gynecological malignancies

Pregnancy should always be ruled out by β-hCG before CT of a female pelvis (or any organ system) is performed
Sonohysterogram
• saline infusion sonohysterogram involves instilling fluid into the uterine cavity transcervically to provide enhanced endometrial visualization during transvaginal U/S examination
• indications: abnormal uterine bleeding, uterine cavity abnormalities that are suspected or noted on transvaginal U/S (e.g. leiomyomas, polyps, synechiae), congenital abnormalities of the uterine cavity, infertility, recurrent pregnancy loss
• contraindications: pregnancy, pelvic infection

<table>
<thead>
<tr>
<th>Table 15. Typical and Atypical Findings on a Sonohysterogram</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finding</strong></td>
</tr>
<tr>
<td>Polyps</td>
</tr>
<tr>
<td>Leiomyoma</td>
</tr>
<tr>
<td>Hyperplasia and Cancer</td>
</tr>
<tr>
<td>Adhesions</td>
</tr>
</tbody>
</table>

Adrenal Mass
• imaging modality: most often identified on CT scan as ‘incidentaloma’, can also use CT/MRI to distinguish benign from malignant masses

<table>
<thead>
<tr>
<th>Table 16. Adrenal Mass Findings on CT and MRI</th>
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</thead>
<tbody>
<tr>
<td><strong>Factors</strong></td>
</tr>
<tr>
<td>Diameter (CT)</td>
</tr>
<tr>
<td>Shape (CT)</td>
</tr>
<tr>
<td>Texture (CT)</td>
</tr>
<tr>
<td>Vascularity (CT)</td>
</tr>
<tr>
<td>Washout of Contrast Medium on CT</td>
</tr>
<tr>
<td>Growth</td>
</tr>
<tr>
<td>Other Findings</td>
</tr>
<tr>
<td>MRI on T2 Weighted Imaging</td>
</tr>
</tbody>
</table>

Neuroradiology

Modalities
• CT is the modality of choice for most neuropathology; even under circumstances when MRI is preferred, CT is frequently the initial study because of its speed, availability, and lower cost
  ▪ acute head trauma: CT is best for visualizing “bone and blood”; MRI is used only when CT fails to detect an abnormality despite strong clinical suspicion
  ▪ acute stroke: MRI ideal, CT most frequently used
  ▪ suspected subarachnoid or intracranial hemorrhage
  ▪ meningitis: rule out mass effect (e.g. cerebral herniation, shift) prior to lumbar puncture
  ▪ tinnitus and vertigo: CT and MRI are used in combination to detect bony abnormalities and CN VIII tumors, respectively
Skull Films
• rarely performed, generally not indicated for non-penetrating head trauma
• indications: screening for destructive bony lesions (e.g. metastases), metabolic disease, skull anomalies, post-operative changes and confirmation of hardware placement, skeletal surveys

CT
• excellent study for evaluation of bony abnormalities
• often done first without and then with IV contrast to show vascular structures or anomalies
• vascular structures and areas of blood-brain barrier impairment are opaque (e.g. hyperattenuating or white/show enhancement) with contrast injection
  ▪ when in doubt, look for circle of Willis or confluence of sinuses to determine presence of contrast enhancement
• posterior fossa can be obscured by extensive bony artifact
• rule out skull fracture, epidural hematoma (lenticular shape), subdural hematoma (crescentic shape), subarachnoid hemorrhage, space occupying lesion, hydrocephalus, and cerebral edema
• multiplanar imaging can be performed with newer generation of multidetector CT scanners

Myelography
• introduction of water-soluble, low-osmotic contrast media into subarachnoid space using lumbar puncture followed by x-ray or CT scan
• indications: excellent study for disc herniations, traumatic nerve root avulsions, patients with contraindication to MRI

MRI
• indications: shows brain and spinal soft tissue anatomy in fine detail, clearly distinguishes white from gray matter (especially T1-weighted series), multiplanar reconstruction helpful in pre-operative assessment

Cerebral Angiography/CTA/MRA
• indications: evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissection
• conventional DSA remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (femoral) puncture; catheter manipulation has risk of vessel injury (e.g. dissection, occlusion, vasospasm, emboli)
• MRA methods (phase contrast, time of flight, gadolinium-enhanced) and CTA are much less invasive without actual risk to intracranial or neck vessels
• MRA and CTA are often used first as ‘screening tests’ for the assessment of subarachnoid hemorrhage, vasospasm, aneurysms

Table 17. Two Types of Hydrocephalus

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicating/Extra-Ventricular</td>
<td>Obstruction distal to the ventricles (e.g. at the level of the arachnoid granulations); imaging shows all ventricles dilated</td>
</tr>
<tr>
<td>Non-Communicating</td>
<td>Obstruction within the ventricular system (e.g. mass obstructing the aqueduct or foramen of Monro); imaging shows dilatation of ventricles proximal to the obstruction</td>
</tr>
</tbody>
</table>

Nuclear Medicine
• SPECT using $^{99m}Tc$-exametazime (HMPAO) and $^{99m}Tc$-bicisate (ECD) imaging assesses cerebral blood flow by diffusing rapidly across the blood brain barrier and becoming trapped within cells
• $^{18}F$DG PET imaging assesses cerebral metabolic activity
Approach to CT Head

- think anatomically, work from superficial to deep
- scan: confirm that the imaging is of the correct patient, whether contrast was used, if the patient is aligned properly, if there is artifact present
- skin/soft tissue: examine the soft tissue superficial to the skull, looking for thickening suggestive of hematoma or edema; also investigate ear, orbital contents (globe, fat, muscles), parotid, muscles of mastication (masseter, temporalis, pterygoids), visualized pharynx
- bone and airspace (use the bone window): check calvarium, visualize mandible, visualize C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for opacity that may suggest fluid, pus, blood, tumor, or fracture; status of the orbital floor in cases of facial trauma (coronal series best)
- dura and subdural space: crescent-shaped hyperdensity in the subdural space suggests subdural hematoma; lentiform hyperdensity in the epidural space suggests epidural hematoma; check symmetry of dural thickness, where increased thickness may suggest the presence of blood
- parenchyma: asymmetry of the parenchyma suggests midline shift; poor contrast between gray and white matter suggests possible infarction, tumor, edema, infection, or contusion; hyperdensity in the parenchyma suggests enhancing lesions, intracerebral hemorrhage, or calcification; central gray matter nuclei (e.g. globus pallidus, putamen, internal capsule) should be visible, otherwise, suspect infarct, tumor, or infection
- ventricles/sulci/cisterns: examine position of ventricles for evidence of midline compression/shift; hyperdensities in the ventricles suggest ventricular/subdural hemorrhage; enlarged ventricles suggest hydrocephalus; obliteration of sulci may suggest presence of edema causing effacement, possible blood filling in the sulci, or tumor; cistern hyperdensities may suggest blood, pus, or tumor

Selected Pathology

- see Neurosurgery NS4-22 for intracranial mass lesions
- see Neurosurgery NS29 and Plastic Surgery PL28 for head trauma
- see Emergency Medicine ER9 for vertebral trauma
- see Neurosurgery NS23-27 and Orthopedics OR21 for degenerative spinal abnormalities

Cerebrovascular Disease (see Neurology N43 and Neurosurgery NS17)

- pathogenesis of stroke: see Neurology N47
- best imaging modality: infarcts best detected by either CT or MRI
- findings of infarction
  - early changes
    - CT
      - usually normal within 6 h of infarction
      - edema (loss of gray-white matter differentiation - “insular ribbon” sign, effacement of sulci, mass effect)
      - within 24 h, loss of low-density, wedge-shaped area of infarction extending to periphery (correlating to vascular territory distal to affected artery)
      - in case of ischemic stroke, may see hyperattenuating (bright) artery (hypodense MCA sign) representing intravascular thrombus or embolus
      - in case of hemorrhagic stroke or transformation (common in basal ganglia and cortex), may see bright acute blood surrounded by edema
    - MRI
      - edema with high signal on T2-weighted images and FLAIR image (loss of gray-white matter differentiation, effacement of sulci, mass effect)
      - DWI shows acute high signal changes demonstrating restricted movement of water indicative of cytotoxic edema; usually indicates stroke damage before CT
      - apparent diffusion coefficient image shows low signal intensity in acute ischemia (nadir 3-5 d, returns to baseline 1-4 wk)
  - subacute changes on CT and MRI
    - edema and mass effect more prominent
    - gyrinal enhancement with contrast indicative of blood-brain barrier breakdown
  - chronic changes on CT and MRI
    - encephalomalacia (parenchymal volume loss) with dilatation of adjacent ventricles
- carotid artery disease
  - best imaging modality: Duplex Doppler U/S
  - other modalities: MRA or CTA if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)
Multiple Sclerosis (refer to Neurology, N52)
- best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
- findings
  - characteristic lesion on MRI is cerebral or spinal plaque
  - plaques typically found in periventricular region, corpus callosum (arranged at right angles to the corpus callosum), centrum semiovale, and to a lesser extent in deep white matter structures and basal ganglia
  - “Dawson’s fingers” refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  - plaques usually have ovoid appearance, hyperintense on T2 and hypointense on T1
  - conventional T2 may underestimate plaque size and overall plaque burden – advanced techniques (diffusion tensor imaging and MR spectroscopy) can be of use
  - perivascular and interstitial edema may be prominent
  - spinal cord lesions typical of MS
    - little or no cord swelling
    - unequivocal hyperintensity on T2-weighted sequences
    - size at least 3 mm but less than 2 vertebral segments in length
    - occupy only part of the cord in cross-section
    - focal (i.e. clearly delineated and circumscribed on T2-weighted sequences)

CNS Infections
- leptomeningitis
  - pathogenesis: inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via organisms gaining access across areas not protected by the blood-brain barrier (choroid plexus or circumventricular organs)
  - pathogens include: S. pneumoniae, H. influenzae, N. meningitidis, L. monocytogenes
  - best imaging modality: MRI (T2-weighted/FLAIR) superior to CT
  - findings
    - meningeal enhancement (following the gyri/sulci, and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
    - a normal MRI does not rule out leptomeningitis
- herpes simplex encephalitis (see Infectious Diseases, ID20)
  - pathogenesis: inflammation of the brain parenchyma secondary to infection with herpes simplex virus, asymmetrically affects the limbic regions of the brain (i.e. temporal lobes, orbitofrontal region, insula, and cingulate gyrus)
  - best imaging modality: MRI (T1- and T2-weighted)
  - findings
    - acute (within 4-5 d): asymmetric high intensity lesions on T2 MRI in temporal and inferior frontal lobes strongly suggestive
    - DDx: infarct, tumor, status epilepticus, limbic encephalitis
    - CT may show low density in temporal lobe and insula; rarely basal ganglia involvement
    - long-term may show parenchymal loss to affected areas
- cerebritis/cerebral abscess
  - pathogenesis: an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms, commonly located in the distribution of the MCA
  - pathogens include: S. aureus (often in IV drug users, nosocomial), Streptococcus, Gram negative bacteria, Bacteroides
  - best imaging modality: MRI including DWI imaging series (abscess will be DWI positive); CT still used as a viable alternative
  - findings according to one of four stages of abscess formation:
    - early cerebritis (1-3 d): inflammatory infiltrate with necrotic center, low intensity on T1, high intensity on T2
    - late cerebritis (4-9 d): ring enhancement may be present
    - early capsule (10-13 d): ring enhancement
    - late capsule (14 d or greater): well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperintensity on T2
Modalities

Plain Film/X-Ray
• usually initial study used in evaluation of bone and joint disorders
• indications: fractures and dislocations, arthritis, assessment of malalignment, orthopedic hardware, and bone tumors (initial)
• minimum of two films orthogonal to each other (usually AP and lateral) to rule out a fracture
• image proximal and distal joints (particularly important with paired bones (e.g. radius/ulna)
• minimally effective in evaluating soft tissue injury
• advantages: fast, inexpensive, readily available, reproducible

CT
• evaluation of fine bony detail
• indications: assessment of complex, comminuted, intra-articular or occult fractures including distal radius, scaphoid, skull, spine, acetabulum, calcaneus, and sacrum
• evaluation of soft tissue calcification/ossification
• advantages: fast, reproducible, excellent bone evaluation, and spatial resolution
• disadvantages: radiation dose, relatively poor soft tissue characterization in comparison with U/S and MRI

MRI
• indications: evaluation of internal derangement of joints (e.g. ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses
• advantages: excellent soft tissue contrast, multiplanar imaging, no radiation
• disadvantages: long imaging times, expensive, claustrophobia, contraindications (e.g. pacemakers, orbital metallic bodies), artifact around metal hardware

U/S
• indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection of soft tissue masses and to determine whether cystic or solid, detection of foreign bodies, U/S guided biopsy and injections
• Doppler determines vascularity of structures
• advantages: good soft tissue evaluation, easy contralateral comparison, dynamic imaging
• disadvantages: operator dependent, poor for bone evaluation

Nuclear Medicine (Bone Scintigraphy)
• determine the location and extent of bony lesions
• 99mTc-methylene diphosphonate localizes to areas of increased bone turnover or calcification – growth plate in children, tumors, infections, fractures, metabolic bone disease (e.g. Paget's), sites of reactive bone formation, and periostitis
• advantages: very sensitive, capable of imaging entire body with relatively low dose radiation
• disadvantages: low specificity, not widely available due to special requirements (e.g. gamma camera, radiopharmaceuticals)

Approach to Interpretation of Bone X-Rays
• identification: name, MRN, age of patient, type of study, region of investigation
• soft tissues: swelling, calcification/ossification
• joints: alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, and symmetry of affected joint
• bone: periosteum, cortex, medulla, trabeculae, density, articular surfaces, bone destruction, bone production, appearance of the edges or borders of any lesions

Trauma

Fracture/Dislocation
• description of fractures
• site of fracture (bone, region of bone, intra-articular vs. extra-articular)
• pattern of fracture line (simple vs. comminuted)
• displacement (distal fragment with reference to the proximal fragment)
Arthritis

Radiographic Hallmarks of Osteoarthritis
- joint space narrowing – typically non-uniform
- subchondral sclerosis
- subchondral cyst formation
- osteophytes

Radiographic Hallmarks of Rheumatoid Arthritis
- joint space narrowing – typically uniform
- soft tissue swelling
- erosions
- periarticular osteopenia

Bone Tumor

Approach
- metastatic tumors to bone are much more common than primary bone tumors, particularly if age >40 yr
  - diagnosis usually requires a biopsy if primary not located
  - few benign tumors/lesions have potential for malignant transformation
  - MRI is good for tissue delineation and pre-operative assessment of surrounding soft tissues, neurovascular structures, and medullary/marrow involvement
  - plain film is less sensitive than other modalities but useful for assessing aggressiveness and constructing differential diagnosis

Considerations and Tumor Characteristics
- for specific bone tumors, see Orthopedics, OR43
- age – most common tumors by age group
  - <1 yr of age: metastatic neuroblastoma
  - 1-20 yr of age: Ewing’s sarcoma in tubular bones
  - 10-30 yr of age: osteosarcoma and Ewing’s sarcoma in flat bones
  - >40 yr of age: metastases, multiple myeloma, and chondrosarcoma
- multiplicity: metastases, myeloma, lymphoma, fibrous dysplasia, enchondromatosis
- location within bone
  - epiphysis: giant cell tumor, chondroblastoma, geode, eosinophilic granuloma, infection
  - metaphysis: simple bone cyst, aneurysmal bone cyst, enchondroma, chondromyxoid fibroma, nonossifying fibroma, osteosarcoma, chondrosarcoma
  - diaphysis: fibrous dysplasia, aneurysmal bone cyst, brown tumors, eosinophilic granuloma, Ewing’s sarcoma
- expansile
  - aneurysmal bone cyst, giant cell tumor, enchondromas, brown tumors, metastases (especially renal and thyroid), plasmacytoma
- matrix mineralization
  - chondroid (popcorn calcification) or osseous
- margin/zone of transition: area between lesion and normal bone
- cortex: intact, disturbed
- periosteal reaction
- soft tissue mass

Benign Lesions which may have Aggressive Features
- Osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Myositis ossificans

Periosteal Reaction
- “Onion skinning” = Ewing’s sarcoma
- “Sunburst”, “hair on end” = osteosarcoma
- “Codman’s triangle” = osteosarcoma, Ewing’s sarcoma, subperiosteal abscess

Figure 37. X-ray of first carpometacarpal joint: normal image (left) and osteoarthritis (right) with joint space narrowing and subchondral sclerosis

Figure 38. Rheumatoid arthritis (A) compared with osteoarthritis (B) changes on X-ray

Figure 39. Radiographic appearance of bone remodelling and destruction processes
Table 18. Characteristics of Benign and Malignant Bone Lesions

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin sclerotic margin/sharp delineation</td>
<td>Poor delineation – wide zone of transition</td>
</tr>
<tr>
<td>Overlying cortex intact</td>
<td>Loss of overlying cortex/bony destruction</td>
</tr>
<tr>
<td>No or simple periosteal reaction</td>
<td>Periosteal reaction</td>
</tr>
<tr>
<td>No soft tissue mass</td>
<td>Soft tissue mass</td>
</tr>
</tbody>
</table>

Metastatic Bone Tumors
- all malignancies have potential to metastasize to bone
- metastases are 20-30x more common than primary bone tumors
- metastasis can cause a lytic or a sclerotic reaction when seeding to bone
- when a primary malignancy is first detected, a bone scan is often part of the initial workup
- may present with pathological fractures or pain
- biopsy or determination of primary is the only way to confirm the diagnosis
- most common metastatic bone tumors: breast, prostate, lung, see Orthopedics, OR46

Table 19. Characteristic Bone Metastases of Common Cancers

<table>
<thead>
<tr>
<th>Lytic</th>
<th>Sclerotic</th>
<th>Expansile</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Prostate</td>
<td>Thyroid</td>
<td>Kidney</td>
</tr>
<tr>
<td>Lung</td>
<td>Breast</td>
<td>Renal</td>
<td>Lung</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Lymphoma</td>
<td>Thyroid</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Kidney</td>
<td>Lung</td>
<td>Thyroid</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bowel</td>
<td>Medulloblastoma</td>
<td>Renal (KLM: flies to the periphery)</td>
</tr>
</tbody>
</table>

Infection

Osteomyelitis
- MRI is the imaging modality of choice for demonstrating bone, bone marrow, and soft tissue abnormalities
- ⁹⁹ᵐTc, followed by ¹¹¹In labeled white cell scan or gallium radioisotope scan
- plain film
  - visible 8-10 d after process has begun
  - osteomyelitic changes on plain film
    - soft tissue swelling
    - local periosteal reaction
    - pockets of air (from anaerobes) may be seen in the tissues, may also suggest necrotizing fasciitis
    - mottled and nonhomogeneous with a classic “moth-eaten” appearance
    - cortical destruction

Bone Abscess
- overlying cortex has periosteal new bone formation
- sharply outlined radiolucent area with variable thickness in zone of transition
- variable thickness periosteal sclerosis
- sequestrum: a piece of dead bone within a Brodie’s abscess
- a sinus tract or cloaca may communicate between the abscess through the cortex to the surface of the bone
- best modality: MRI for bone, bone marrow, and soft tissue abnormalities; CT for sequestra and cortical erosions

Metabolic Bone Disease

Osteoporosis
- reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
- DEXA: gold standard for measuring bone mineral density
  - T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - osteopenia: –2.5 < T-score < –1
    - osteoporosis: T-score ≤–2.5
  - Z-score: the number of standard deviations from the age-matched mean
  - risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy

Diagnostic sensitivity of DEXA highest when bone mineral density measured at lumbar spine and proximal femur
• appearance on plain film
  ▪ osteopenia: reduced bone density on plain films
  ▪ may also be seen with osteomalacia, hyperparathyroidism, and disuse
  ▪ compression of vertebral bodies
  ▪ biconcave vertebral bodies (“codfish” vertebrae)
  ▪ long bones have appearance of thinned cortex and increased medullary cavity
  ▪ look for complications of osteoporosis (e.g. insufficiency fractures: hip, vertebral, sacrum, pubic rami)
• see Endocrinology, E42

Osteomalacia/Rickets
• reduction in bone mineral density, usually due to vitamin D deficiency, resulting in softening and bowing of long bones
• similar to osteoporosis, initial radiological appearance of osteopenia (coarse and poorly defined bone texture)
• “fuzzy”, ill-defined trabeculae
• Looser’s zones (pseudofracture)
  ▪ characteristic radiologic feature
  ▪ fissures or clefts at right angles to long bones and extending through cortex
• DDx: chronic renal disease, fibrous dysplasia, hyperthyroidism, Paget’s, osteodystrophy, X-linked hypophosphatemia

Hyperparathyroidism
• most common cause is renal failure (secondary hyperparathyroidism)
• chondrocalcinosis
  ▪ calcium crystal deposition in hyaline cartilage or fibrocartilage (including arteries and periarticular soft tissue)
  ▪ resorption of bone typically in hands (subperiosteal and at tufts), sacroiliac joints (subchondral), skull (“salt and pepper” appearance), osteoclastoma (brown tumors)
  ▪ “rugger jersey spine”: band-like osteosclerosis at superior/inferior margins of vertebral bodies
• see Endocrinology, E45

Paget’s Disease
• abnormal remodeling involving single or multiple bones – especially skull, spine, pelvis
• 3 phases: 1st phase = lytic, 2nd phase = mixed (lytic/sclerotic), 3rd phase = sclerotic
• features
  ▪ coarsening of the trabeculae with bone expansion
  ▪ bone softening/bowing
  ▪ bone scan will reveal high activity, especially at bone ends
  ▪ thickened cortex
• see Endocrinology, E46
Nuclear Medicine

Brain

- $^{99m}$Tc-HMPAO and $^{99m}$Tc-ECD imaging to assess cerebral blood flow, taken up in cortical and subcortical gray matter; used for dementia, traumatic brain injury and to a lesser extent vasculitis, neuropsychiatric disorders and stroke
- PET imaging assesses metabolic activity by using $^{18}$FDG
- CSF imaging, intrathecal administration of $^{111}$In DTPA to evaluate CSF leak or to differentiate normal pressure hydrocephalus from other causes of hydrocephalus
- Ventricular shunt evaluation for obstruction (most commonly ventriculoperitoneal) with $^{99m}$Tc or $^{111}$In-DTPA

Thyroid

Radioactive Iodine Uptake (see Endocrinology, E21)
- index of thyroid function (trapping and organification of iodine)
- radioactive $^{123}$I or $^{125}$I given PO to fasting patient
- measure percentage of administered iodine taken up by thyroid
- increased RAIU: toxic multinodular goitre, toxic adenoma, Graves’ disease
- decreased RAIU: subacute thyroiditis, late Hashimoto’s disease, hormone suppression
- falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed)

Thyroid Imaging (Scintiscan)
- $^{99m}$Tc/pertechnetate IV or radioactive iodine ($^{123}$I)
- provides functional anatomic detail
- hot (hyperfunctioning) lesions: usually benign (e.g. adenoma, toxic multinodular goitre), cancer very unlikely (less than 1%)
- cold (hypofunctioning) lesions: cancer must be considered until biopsy negative even though only 6-10% are cancerous
- isointense lesions: cancer must be considered as an isointense lesion may represent cold nodules superimposed on normal tissue; if cyst suspected, correlate with U/S
- serum thyroglobulin to detect recurrent thyroid cancer post-treatment

Radioiodine Ablation
- $^{123}$I for Graves’ disease, multinodular goitre, thyroid cancer

Respiratory

V/Q Scan

- examine areas of lung in which ventilation and perfusion do not match
- ventilation scan
  - patient breathes radioactive gas ($^{99m}$Tc-DTPA, $^{133}$Xe, Technegas) through a closed system, filling alveoli proportionally to ventilation
  - ventilation scan defects indicate: airway obstruction, chronic lung disease, bronchospasm, tumor mass obstruction
- perfusion scan
  - radiotracer injected IV ($^{99m}$Tc-MAA) \( \rightarrow \) trapped in pulmonary capillaries (1 in 1500 arterioles occluded) according to blood flow
  - gives a map of pulmonary circulation
  - relatively contraindicated in severe pulmonary HTN and right-to-left shunt
- with PE
  - areas of lung are well ventilated but not perfused (unmatched defect)
  - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
  - reported as high probability, intermediate, low, very low, or normal
- V/Q scans for PE have been largely replaced by CT scan with contrast (see Respirology, R19)
- not valid for assessment of PE when patients have intrinsic lung diseases and ventilatory problems
- modified V/Q scan (perfusion only, lower dose contrast) may be used for pregnant patients if CXR is normal
Cardiac

Myocardial Perfusion Scanning
- for investigation of angina, atypical chest pain, CAD, and follow-up post-bypass
- thallium-201 (a radioactive analogue of potassium), 99mTc-sestamibi, or 99mTc-tetrofosmin
- injected at peak exercise (physical stress) or after persantine challenge (vasodilator) and again later at rest
- persistent defect (at rest and stress) suggests infarction; reversible defect (only during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- see Cardiology and Cardiac Surgery, C13

Radionuclide Ventriculography
- 99mTc tagged to red blood cells
- first pass through RV → pulmonary circulation → LV; provides information about RV function
- cardiac MUGA scan sums multiple cardiac cycles
- images are obtained by gating (synchronizing) the count acquisitions to the ECG signal
- MUGA scan can be used to study the function of the heart at a particular stage of contraction
- provides information on ejection fraction (normal = 50-65%), ventricular volume, and wall motion

Abdomen and Genitourinary System

HIDA Scan
- IV injection of 99mTc-disofenin (DISIDA) or 99mTc-mebrofenin which is bound to protein, taken up, and excreted by hepatocytes into biliary system
- can be performed in non-fasting state but prefer NPO after midnight
- gallbladder visualized when cystic duct is patent (rules out cholecystitis with >99% certainty), usually seen by 30 min to 1 h
- acute cholecystitis: no visualization of gallbladder at 4 h or after administration of morphine at 30 min
- chronic cholecystitis: no visualization of gallbladder at 1 h but seen at 4 h or after morphine administration
- differential diagnosis of obstructed cystic duct: acute/chronic cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting less than 4 h or more than 24 h
- assess bile leaks post-operatively

RBC Scan
- IV injection of radiotracer with sequential images of the abdomen (99mTc RBCs)
- GI bleed
  - if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed, look for a change in shape and location on sequential image
  - if bleeding acutely at >0.5 mL/min, use angiography (more specific)
- liver lesion evaluation
  - hemangioma has characteristic appearance: cold early, fills in later

Bone

Bone Scan
- isotopes
  - 99mTc-diphosphonate
    - triphasic bone scan: flow → blood pool → delayed bone images
    - uptake can distinguish bone vs. soft tissue infection and septic arthritis vs. osteomyelitis vs. peripheral cellulitis
    - acute osteomyelitis: increased activity in flow, blood pool, and delayed bone images; usually does not cross joint
    - septic arthritis and cellulitis: increased activity in blood pool and normal or slightly increased activity in delayed images; may cross joint
    - 111In WBC: tracks the active migration of the WBC, more specific for infection
    - 67Ga citrate: may see uptake in some tumors, also more specific for infection
- radioactive tracer binds to hydroxyapatite of bone matrix
• increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
• indications: bone pain of unknown origin, avascular necrosis, suspected malignancy, staging malignancy (breast, prostate, kidney or lung), follow up after treatment, detection and follow up of primary bone disease, assessment of skeletal trauma, detection of soft tissue calcification renal failure
• differential diagnosis of positive bone scan: bone metastases (breast, prostate, lung, thyroid), primary bone tumor, arthritis, fracture, infection, anemia, Paget's disease
• multiple myeloma: typically normal or cold (false negative); need a skeletal survey
• "superscan": increased bone uptake and poor renal uptake due to diffuse metastases or metabolic causes (renal osteodystrophy)

**Interventional Radiology**

**Vascular Procedures**

**Angiography**
- injection of contrast material through a catheter placed directly into an artery or vein to delineate vascular anatomy
- catheter can be placed into a large vessel (e.g. aorta, vena cava) for a “flush” or selectively placed into a branch vessel for more detailed examination of smaller vessels and specific organs
- indications: diagnosis of primary occlusive or stenotic vascular disease, aneurysms, coronary, carotid and cerebral vascular disease, PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (endovascular aneurysm repair, thrombolysis, stenting, and angioplasties)
- complications (<5% of patients): puncture site hematoma, infection, pseudoaneurysm, AV fistula, dissection, thrombosis, embolic occlusion of a distal vessel
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (color Doppler U/S, CTA, and MRA)

**Percutaneous Transluminal Angioplasty and Stents**
- introduction and inflation of a balloon into a stenosed vessel to restore distal blood supply
- common alternative to surgical bypass grafting with 5 yr patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary, and carotid artery stenoses are amenable to treatment
- vascular stents may help improve long-term results by keeping the vessel wall patent after PTA
- stents are also used for angioplasty failure or complications
- stent grafts (metal mesh covered with durable fabric) may provide an alternative treatment option for aneurysms and AV fistulas
- complications: similar to angiography, but also includes vessel rupture

**Thrombolytic Therapy**
- may be systemic (IV) or catheter directed
- infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
- can restore blood flow in a vessel obstructed with a thrombus or embolus
- indications: treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of venous thrombosis (DVT or PE)
- complications: bleeding, stroke, distal embolus, reperfusion injury with myoglobinuria and renal failure if advanced ischemia present

**Embolization**
- injection of occluding material into vessels
- permanent agents: amplatz plugs, coils, glue, and onyx
- temporary: gel foam, autologous blood clots
- indications: management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of arteriovenous malformation, pre-operative treatment of vascular tumors (bone metastases, renal cell carcinoma), varicocele embolization for infertility, symptomatic uterine fibroids
- complications: post-embolization syndrome (pain, fever, leukocytosis), unintentional embolization of a non-target organ with resultant ischemia
Inferior Vena Cava Filter
- insertion of metallic "umbrellas" to mechanically trap emboli and prevent PE
- may be temporary (retrievable) or permanent
- inserted via femoral vein, jugular vein, or antecubital vein
- usually placed infrarenally to avoid renal vein thrombosis
- indications: contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation

Central Venous Access
- variety of devices available
- PICC, external tunneled catheter (Hickman or dialysis catheters), subcutaneous port (Portacath®)
- indications: chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
- complications: venous thrombosis and central venous stenosis, infection including sepsis, pneumothorax

Nonvascular Interventions

Percutaneous Biopsy
- replaces open surgical procedure
- many sites are amenable to biopsy using U/S, fluoroscopy or CT guidance
- complications: false negative (sampling error or tissue necrosis), pneumothorax in 30% of lung biopsies (chest tube required in approximately 5%), acute pancreatitis (pancreatic biopsies), bleeding from liver biopsies in patients with uncorrectable coagulopathies or ascites (can be minimized with transjugular approach)

Abscess Drainage
- placement of a drainage catheter into an infected fluid collection
- administer broad spectrum IV antibiotics prior to procedure
- routes: percutaneous (most common), transgluteal, transvaginal, transrectal
- complications: hemorrhage, injury to intervening structures (e.g. bowel), bacteremia, sepsis

Percutaneous Biliary Drainage/Cholecystostomy
- placement of drainage catheter ± metallic stent into obstructed biliary system (PBD) or gallbladder (cholecystostomy) for relief of jaundice or infection
- percutaneous gallbladder access can be used to crush or remove stones
- indications
  - cholecystostomy: acute cholecystitis
  - PBD: biliary obstruction secondary to stone or tumor, cholangitis
- complications
  - acute: sepsis, hemorrhage
  - long-term: tumor overgrowth and stent occlusion

Percutaneous Nephrostomy
- placement of catheter into renal collecting system
- indications: hydronephrosis, pyonephrosis, ureteric injury with or without urinary peritonitis (traumatic or iatrogenic)
- complications: bacteria and septic shock, hematuria due to pseudoaneurysm or AV fistulas, injury to adjacent organs

Gastrostomy/Gastrojejunostomy
- percutaneous placement of catheter directly into either stomach (gastrostomy) or through stomach into small bowel (transgastric jejunostomy)
- indications: inability to eat (most commonly CNS lesion) or esophageal obstruction, decompression in gastric outlet obstruction
- complications: gastroesophageal reflux with aspiration, peritonitis, hemorrhage, bowel or solid organ injury

Radiofrequency Ablation
- U/S or CT guided probe is inserted into tumor, radiofrequency energy delivered through probe causes heat deposition and tissue destruction
- indications: hepatic tumors (HCC and metastases), renal tumors
- complications: destruction of neighbouring tissues and structures, bleeding
Breast Imaging

Modalities

Mammography

Description
• x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities (see General Surgery, GS54)

Indications
• screening
  ▪ begin screening from age 50 q1-2 yr
  ▪ if over the age of 70, continue screening mammography if in good general health
  ▪ not routinely recommended if under the age of 50 unless strong family history
  ▪ if positive family history, begin screening 5-10 yr younger than the first degree relative who developed breast cancer
• diagnostic
  ▪ signs and symptoms suggestive of breast cancer include a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, and spontaneous serous or sanguinous nipple discharge from a single duct
  ▪ women with abnormal screening mammograms
  ▪ follow-up of women with previous breast cancer
  ▪ suspected complications of breast implants

Table 20. Breast Imaging Reporting and Data System (BI-RADS®) Mammography Categories

<table>
<thead>
<tr>
<th>Assessment Categories</th>
<th>Imaging Findings</th>
<th>Follow-up Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS 0</td>
<td>Incomplete</td>
<td>Additional imaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison to prior films</td>
</tr>
<tr>
<td>BI-RADS 1</td>
<td>Negative</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 2</td>
<td>Benign</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 3</td>
<td>Probably benign</td>
<td>Unilateral mammogram at 6 mo</td>
</tr>
<tr>
<td></td>
<td>Likelihood of malignancy is &lt;2%</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 4</td>
<td>Suspicious abnormality</td>
<td>Biopsy</td>
</tr>
<tr>
<td>BI-RADS 5</td>
<td>Highly suspicious of malignancy</td>
<td>Biopsy</td>
</tr>
<tr>
<td></td>
<td>Likelihood of malignancy is 95%</td>
<td></td>
</tr>
<tr>
<td>BI-RADS 6</td>
<td>Malignancy confirmed by biopsy</td>
<td>Definitive therapy</td>
</tr>
</tbody>
</table>

Breast MRI

Description
• should be used only after mammography and U/S investigation
• sensitive for detecting invasive breast cancer (95-100%) but specificity variable (37-97%)
• use as a screening modality has been limited to high risk patients

Indications
• evaluation of previously diagnosed breast cancer: positive margins, recurrence, response to chemotherapy
• post-surgical resection of breast cancer
• known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer
• untested first-degree relative of a carrier of such a gene mutation
• family history consistent with a hereditary breast cancer syndrome and estimated personal lifetime cancer risk >25%
• high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ)
• radiation therapy to chest (before age 30)
• MRI should not be used to screen the general population or to differentiate between benign and malignant lesions
U/S

Definition
• U/S can determine if a mass is cystic or solid and is commonly used during biopsy

Indications
• identification and characterization of palpable abnormalities
• evaluation of ambiguous mammographic findings in the determination of cystic vs. solid characteristics
• evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
• guidance for interventional procedures
• breast U/S is the initial imaging technique to evaluate palpable masses in women under 30 and in lactating and pregnant women

Breast Interventional Procedures

Description
• includes fine needle aspirate biopsy, core needle biopsy, abscess drainage, and cyst aspiration (see General Surgery, GS54)

Indications
• cystic mass: complex cyst, symptomatic, suspected abscess
• solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) or confirm diagnosis of a probable benign mass (BI-RADS® Category 3)
• initial percutaneous biopsy procedure that was insufficient or discordant with imaging
• presurgical U/S-guided localization of a lesion

Breast Findings

Breast Masses
• definition: a space occupying lesion seen in two different projections; if seen in only a single projection it should be called a “density” until its three-dimensionality is confirmed

Table 21. Mammographic Features of Benign and Malignant Breast Masses

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shape</strong></td>
<td>Oval, round, lobular</td>
<td>Irregular</td>
</tr>
<tr>
<td><strong>Margin</strong></td>
<td>Circumscribed, well-defined</td>
<td>Indistinct, microlobulated, spiculated</td>
</tr>
<tr>
<td><strong>Density</strong></td>
<td>Radiolucent (oil cyst, lipoma, fibrolipoma, galactocele, hamartoma)</td>
<td>Radiodense</td>
</tr>
<tr>
<td><strong>Calcifications (± mass)</strong></td>
<td>Popcorn (hyalinizing fibroadenoma), lucent centered (oil cyst/fat necrosis), layering (milk of calcium), vascular, round, scattered</td>
<td>Pleomorphic (vary in size and shape), amorphous (indistinct), fine linear, coarse heterogeneous, regional, segmental, clustered</td>
</tr>
</tbody>
</table>

Other Findings
• tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
• intramammary lymph node: typical lymph nodes are circumscribed, reniform and often have a fatty notch and center; usually less than 1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty center or notch) are well seen, the lesion is almost always benign and insignificant
• focal asymmetric density: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
  ▪ if focal compression shows mass-like character, or if the area can be palpated, biopsy must be considered
References


Canadian Association of Radiologists (CAR) standard for breast imaging. Ottawa: Canadian Association of Radiologists, 1998.


# Nephrology

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Amanda Huynh, Jessica Huynh, and Vahagn Karapetyan, associate editors
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**Basic Anatomy Review**

**Anatomy of the Kidney**

- see Urology, U4

**Renal Structure and Function**

The Nephron
- basic structural and functional unit of the kidney, approximately 1 million per kidney
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

Table 1. Major Functions of the Kidneys

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<th>Function</th>
<th>Mechanism</th>
<th>Affected Elements</th>
</tr>
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<td>1. Waste Excretion</td>
<td>Glomerular filtration</td>
<td>Excretion of nitrogenous products of protein metabolism (urea, Cr)</td>
</tr>
<tr>
<td></td>
<td>Tubular secretion</td>
<td>Excretion of organic acids (urate) and organic bases (Cr)</td>
</tr>
<tr>
<td></td>
<td>Tubular catabolism</td>
<td>Breakdown and excretion of drugs (antibiotics, diuretics) and peptide hormones (most pituitary hormones, insulin, glucagon)</td>
</tr>
<tr>
<td>2. Electrolyte Balance</td>
<td>Tubular NaCl and water reabsorption</td>
<td>Controls volume status and osmolar balance</td>
</tr>
<tr>
<td></td>
<td>Tubular K+ secretion</td>
<td>Controls potassium concentration</td>
</tr>
<tr>
<td></td>
<td>Tubular H+ secretion</td>
<td>Acid-base balance</td>
</tr>
<tr>
<td></td>
<td>HCO3– synthesis and reabsorption</td>
<td>Tubular Ca2+, Mg2+, PO43- transport</td>
</tr>
<tr>
<td></td>
<td>Tubular Ca2+, Mg2+, PO43- transport</td>
<td>Alters Ca2+, Mg2+, PO43- homeostasis</td>
</tr>
<tr>
<td>3. Hormonal Synthesis</td>
<td>Erythropoietin production (cortex)</td>
<td>RBC production</td>
</tr>
<tr>
<td></td>
<td>Vitamin D activation: 25(OH)D converted to 1,25(OH)2D</td>
<td>Calcium homeostasis</td>
</tr>
<tr>
<td></td>
<td>Renin production (juxtaglomerular apparatus)</td>
<td>Alters vascular resistance and aldosterone secretion</td>
</tr>
<tr>
<td>4. Blood Pressure Regulation</td>
<td>Na+ excretion</td>
<td>Alters ECF volume</td>
</tr>
<tr>
<td></td>
<td>Renin production</td>
<td>Alters vascular resistance</td>
</tr>
<tr>
<td>5. Glucose Homeostasis</td>
<td>Gluconeogenesis (from lactate, pyruvate, and amino acids)</td>
<td>Glucose supply maintained in prolonged starvation</td>
</tr>
</tbody>
</table>

The Glomerulus
- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman’s space
- particles are selectively filtered by size (<60 kDa) and charge (negative charge repelled)
- consists of following cell types
  1. Mesangial cells
  - structural cells that support the vascular tree; they are also contractile and produce vasoactive substances to help control blood flow
  2. Capillary endothelial cells
  - one of the cells of the glomerular filtration barrier and help form the plasma filtration apparatus due to their sinusoidal nature and glycocalyx; contribute to the production of the GBM
  3. Visceral epithelium (podocytes)
  - one of the cells of the glomerular filtration barrier and help form the plasma filtration apparatus due to their interdigitated foot process that form slit diaphragms; contribute to the production of the GBM
  4. Parietal epithelium
  - lines the interior of Bowman’s capsule and contains a podocyte progenitor population
  5. Juxtaglomerular cells
  - smooth muscle cell in lining of afferent arteriole; produce, store, and secrete renin as part of renal autoregulation

**Acronyms**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>ACEI</td>
<td>angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACR</td>
<td>albumin to creatinine ratio</td>
</tr>
<tr>
<td>ADH</td>
<td>antidiuretic hormone</td>
</tr>
<tr>
<td>AG</td>
<td>anion gap</td>
</tr>
<tr>
<td>AKI</td>
<td>acute kidney injury</td>
</tr>
<tr>
<td>ANA</td>
<td>antinuclear antibody</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>ASA</td>
<td>acetylsalicylic acid</td>
</tr>
<tr>
<td>ASO</td>
<td>anti-streptolysin O antibody</td>
</tr>
<tr>
<td>ATN</td>
<td>acute tubular necrosis</td>
</tr>
<tr>
<td>AVM</td>
<td>arteriovenous malformation</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>cytoplasmic antineutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>C5b-9</td>
<td>complement component 5b-9</td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CIC</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>Ccr</td>
<td>creatinine clearance</td>
</tr>
<tr>
<td>DI</td>
<td>diabetes insipidus</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-stage renal disease</td>
</tr>
<tr>
<td>FF</td>
<td>filtration fraction</td>
</tr>
<tr>
<td>FGFR</td>
<td>focal segmental glomerulosclerosis</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>GN</td>
<td>glomerulonephritis</td>
</tr>
<tr>
<td>HCT</td>
<td>hematocrit</td>
</tr>
<tr>
<td>HUS</td>
<td>hemolytic uremic syndrome</td>
</tr>
<tr>
<td>IVR</td>
<td>intravenous pyelogram</td>
</tr>
<tr>
<td>MDRD</td>
<td>modification of diet in renal disease</td>
</tr>
<tr>
<td>NS</td>
<td>normal saline</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>perinuclear anti-neutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>PCKD</td>
<td>polycystic kidney disease</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>RTA</td>
<td>renal tubular acidosis</td>
</tr>
<tr>
<td>SIADH</td>
<td>syndrome of inappropriate antidiuretic hormone</td>
</tr>
<tr>
<td>TCT</td>
<td>total cholesterol</td>
</tr>
<tr>
<td>UAG</td>
<td>urine anion gap</td>
</tr>
<tr>
<td>UTI</td>
<td>urinary tract infection</td>
</tr>
</tbody>
</table>
Figure 1. The glomerulus

The Renal Tubules

- Reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion
- Each segment of the tubule selectively transports various solutes and water and is targeted by specific diuretics
Renal Hemodynamics

- GFR
  - the rate of fluid transfer between glomerular capillaries and Bowman’s space
  - 180 L/d, of which 99% is reabsorbed, giving a daily urine output of 1.0-1.5 L
  - normal urine output is >0.5 ml/kg/h in adults
  - GFR is highest in early adulthood, and decreases thereafter
- renal autoregulation maintains constant GFR over mean arterial pressures of 70-180 mmHg
- 2 mechanisms of autoregulation:
  - myogenic mechanism: release of vasoactive factors in response to changes in perfusion pressure (e.g. ↑ perfusion pressure → afferent arteriolar constriction → ↓ GFR)
  - tubuloglomerular feedback: changes in Na⁺ delivery to macula densa lead to changes in afferent arteriolar tone (e.g. increased delivery causes afferent constriction)
- FF
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio: FF = GFR/RPF; normal = 0.2 or 20%
  - angiotensin II constricts renal efferent arterioles, which increases FF thereby maintaining GFR
- renin is released from juxtaglomerular apparatus in response to decreased RPF

Assessment of Renal Function

Measurement of Renal Function

- GFR = rate of filtration of plasma by the glomeruli
- most renal functions decline in parallel with a decrease in GFR
- insulin clearance is the gold standard for measuring GFR, but very rarely used clinically
- clinically, GFR is estimated using serum creatinine concentration, [Cr]
- Cr is a metabolite of creatine (intermediate in muscle energy metabolism)
- Cr is freely filtered at the glomerulus with no tubular reabsorption
- tubular secretion varies based on level of renal function (10% to >50%)
- rate of production determined by muscle mass
- Cr filtered = Cr excreted (at steady state)

Ways to Estimate GFR Using Serum Creatinine Concentration

1. Measure CrCl
   - calculation provides reasonable estimate of GFR
   - measure plasma [Cr], 24 h urine volume, and urine [Cr]
   - GFR/d = (urine [Cr] x urine volume/d)/(plasma [Cr])
   - must use same units for urine [Cr], and plasma [Cr]
2. Estimate CrCl using Cockcroft-Gault formula
   - serum Cr used along with age, gender, and weight (kg) to estimate GFR
   - normal range is >90 mL/min (>1.5 mL/s)
3. Estimate GFR using MDRD formula
   - most common way in which GFR is estimated (MDRD 7 equation)
   - complex formula incorporating age, gender, serum Cr, and African descent, but does not include weight
   - GFR is reported as mL/min/1.73 m² body surface area

4. Estimate GFR using CKD-EPI equation
   - the best current equation
   - calculated using serum Cr, age, sex, and race

Limitations of Using Serum Cr Measurements
1. must be in steady state
   - constant GFR and rate of production of Cr from muscles
   - sudden injury may reduce GFR substantially, but it takes time for Cr to accumulate and then re-establish steady state
   - clinical correlation: in AKI, the rise in Cr is often delayed
2. GFR must fall substantially before plasma [Cr] rises above normal laboratory range
   - with progressive renal failure, remaining nephrons compensate with hyperfiltration
   - GFR is relatively preserved despite significant structural damage
3. plasma [Cr] is influenced by the rate of Cr production
   - lower production with smaller muscle mass (e.g. female, elderly, low weight)
   - for example, consider plasma [Cr] of 100 µmol/L (1.13 mg/dL) in both of these patients
     - 20 yr old man who weighs 100 kg, GFR = 144 mL/min
     - 80 yr old woman who weighs 50 kg, GFR = 30.6 mL/min
   - clinical correlation: GFR decreases with age but would not be reflected as a rise in serum Cr due to the age-associated decline in muscle mass
4. tubular secretion of Cr increases as GFR decreases
   - serum Cr and CrCl overestimate low GFR
   - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
5. errors in Cr measurement
   - very high bilirubin level causes [Cr] to be falsely low
   - acetooacetate (a ketone body) and certain drugs (cefoxitin) create falsely high [Cr]

Measurement of Urea Concentration
- urea is the major end-product of protein metabolism
- plasma urea concentration reflects renal function but should not be used alone as it is modified by a variety of other factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or catabolism (sepsis, trauma, GI bleed) causes urea level to rise
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in hypernatremic states such as ECF volume depletion
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mEq/L for urea and µmol/L for Cr)

Urinalysis
- use dipstick in freshly voided urine specimen to assess the following:

1. Specific Gravity
   - ratio of the mass of equal volumes of urine/H₂O
   - range is 1.001 to 1.030
   - values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
   - value usually 1.010 in ESRD (isosthenuria)

2. pH
   - urine pH is normally between 4.5-7.0; if persistently alkaline, consider:
     - RTA
     - UTI with urease-producing bacteria (e.g. Proteus)

3. Glucose
   - freely filtered at glomerulus and reabsorbed in proximal tubule
   - causes of glucosuria include
     - hyperglycemia >160-200 mg/dL (>9.11 mEq/L) leads to filtration that exceeds tubular resorption capacity
     - increased GFR (e.g. pregnancy)
     - proximal tubule dysfunction (e.g. Fanconi’s syndrome)

4. Protein
   - dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
   - microalbuminuria (defined as ≥2.0 mg/mEq Cr in males and ≥2.8 mg/mEq Cr in females) is not detected by standard dipstick (see Diabetes, NP28)
   - sulfosalicylic acid detects all protein in urine by precipitation
   - gold standard: 24 h timed urine collection for total protein
   - Limitations of Using Serum Cr Measurements
     - serum Cr and CrCl overestimate low GFR
     - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
     - very high bilirubin level causes [Cr] to be falsely low
     - acetooacetate (a ketone body) and certain drugs (cefoxitin) create falsely high [Cr]
5. Leukocyte Esterase
- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation (e.g. AIN)

6. Nitrites
- nitrates in urine are converted by some bacteria to nitrites
- high specificity, low sensitivity for UTI

7. Ketones
- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

8. Hemoglobin
- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis), and true hematuria (RBCs seen on microscopy)

### Urine Microscopy

- centrifuge urine specimen for 3-5 min, discard supernatant, resuspend sediment and plate on slide
- shaking tube vigorously may disrupt casts

<table>
<thead>
<tr>
<th>Active Sediment = Suggestive of Parenchymal Kidney Disease</th>
<th>Bland Sediment = Less Likely Parenchymal Kidney Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any one or more of the following seen on microscopy</td>
<td></td>
</tr>
<tr>
<td>Red cell casts</td>
<td>Only hyaline casts</td>
</tr>
<tr>
<td>White cell casts</td>
<td>≤ 2 red cells per HPF</td>
</tr>
<tr>
<td>Muddy-brown granular or epithelial cell casts</td>
<td>≤ 4 white cells per HPF</td>
</tr>
<tr>
<td>&gt; 2 red cells per HPF</td>
<td>Small quantities of crystals</td>
</tr>
<tr>
<td>&gt; 4 white cells per HPF</td>
<td>Small amount of bacteria</td>
</tr>
</tbody>
</table>

### 1. CELLS

Erythrocytes
- normal range = up to 2-3 RBCs per HPF
- hematuria = greater than 2-3 RBCs per HPF
- dysmorphic RBCs and/or RBC casts suggest glomerular bleeding (e.g. proliferative GN)
- isomorphic RBCs, no casts suggest extraglomerular bleeding (e.g. bladder Ca)

Leukocytes
- normal range = up to 3 WBCs per HPF
- pyuria = greater than 3 WBCs per HPF
- indicates inflammation or infection
- if persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, papillary necrosis, renal TB, viral infections

Eosinophils
- detected using Wright’s or Hansel’s stain (not affected by urine pH)
- consider AIN, atheroembolic disease

Oval Fat Bodies
- renal tubular cells filled with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

### 2. CASTS
- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein

<table>
<thead>
<tr>
<th>Table 3. Interpretation of Casts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaline casts</td>
</tr>
<tr>
<td>RBC casts</td>
</tr>
<tr>
<td>WBC casts</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pigmented granular casts</td>
</tr>
<tr>
<td>(heme granular casts, muddy brown)</td>
</tr>
<tr>
<td>Fatty casts</td>
</tr>
</tbody>
</table>
3. CRYSTALS

- uric acid: consider acid urine, hyperuricosuria
- calcium phosphate: alkaline urine
- calcium oxalate: consider hyperoxaluria, ethylene glycol poisoning
- sulfur: sulfa-containing antibiotics

**Urine Biochemistry**

- commonly measure: Na⁺, K⁺, Cl⁻, osmolality, and pH
- no ‘normal’ values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient's current state

1. ECF volume depletion: expect low urine [Na⁺] (kidneys should be retaining Na⁺)
   - urine [Na⁺] (>40 mEq/L) suggests a renal problem or the action of a diuretic
   - urine [Na⁺] (<20 mEq/L) suggests a prerenal problem
2. daily urinary potassium excretion rate should be decreased (<20 mEq/d) in hypokalemia
   - if higher than 20 mEq/d, suggests renal contribution to hypokalemia
- osmolality is useful to estimate the kidney's concentrating ability
- FENa refers to the fractional excretion of Na⁺
  - FENa = urine [Na⁺] x plasma [Cr] / (plasma [Na⁺] x urine [Cr])
  - FENa <1% suggests the pathology is prerenal

**Examples of Common Urine Electrolyte Abnormalities**

- high urine [Na⁺] (>40 mEq/L) in the setting of AKI: suggests renal disease
- high urine [Na⁺] (>40 mEq/L) in the setting of hyponatremia: generally from causes such as diuretics, tubular disease (e.g. Bartter’s syndrome), SIADH
- additionally, urine pH is useful to grossly assess renal acidification
  - low pH (<5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (e.g. RTA)

**Electrolyte Disorders**

**Sodium Homeostasis**

- hyponatremia and hypernatremia are disorders of water balance
  - hyponatremia usually suggests too much water in the ECF relative to Na⁺
  - hypernatremia usually suggests too little water in the ECF relative to Na⁺
- solutes (such as Na⁺, K⁺, glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
  - water moves out of cells in response to increased ECF osmolality
  - water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by Na⁺ content rather than concentration
- Na⁺ deficiency leads to ECF volume contraction
- Na⁺ excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially in the brain) shrinking (hyponatremia) or swelling (hyponatremia)

**Table 4. Clinical Assessment of ECF Volume (Total Body Na⁺)**

<table>
<thead>
<tr>
<th>Fluid Compartment</th>
<th>Hypovolemic</th>
<th>Hypervolemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>JVP</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Orthostatic drop</td>
<td>Normal to increased</td>
</tr>
<tr>
<td>Auscultation of heart</td>
<td>Tachycardia</td>
<td>S3</td>
</tr>
<tr>
<td>Auscultation of lungs</td>
<td>Normal</td>
<td>Inspiratory crackles</td>
</tr>
<tr>
<td>Interstitial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin turgor</td>
<td>Decreased</td>
<td>Normal/Increased</td>
</tr>
<tr>
<td>Edema (dependent)</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td>Decreased*</td>
<td>Variable</td>
</tr>
<tr>
<td>Body weight</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Hematocrit, serum protein</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

*If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia
# Hyponatremia

- Hyponatremia: serum [Na⁺] <135 mEq/L.
- Can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality.
- Consider if it is "appropriate" vs. "inappropriate" ADH secretion.
- If appropriate ADH secretion, is it real vs. effective volume loss?

**Figure 4. Approach to hyponatremia**

### Signs and Symptoms
- Depend on degree of hyponatremia and more importantly, velocity of progression from onset.
- Acute hyponatremia (<24-48 h) more likely to be symptomatic.
- Chronic hyponatremia (>24-48 h) less likely to be symptomatic due to adaptation.
  - Adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days).
  - Adaptation is responsible for the risks associated with overly rapid correction.
- Neurologic symptoms predominate (secondary to cerebral edema): headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased LOC.

### Complications
- Seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death.
- Risk of brain cell shrinkage with rapid correction of hyponatremia.
  - Can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible.
  - (e.g. central pontine myelinolysis: cranial nerve palsies, quadriplegia, decreased LOC).

### Risk Factors for Osmotic Demyelination
- Rise in serum [Na⁺] with correction >8 mEq/L/d if chronic hyponatremia.
- Associated hypokalemia.
- If patient with hyponatremia and hypovolemia is given large volumes of isotonic fluids that do not contain sodium (e.g. mannitol).
- Diuretics (especially thiazides), salt-wasting nephropathy.
- Diarrhea, excess sweating, third spacing (e.g. peritonitis, pancreatitis, burns).

### Investigations
- ECF volume status assessment (see Table 4).
- Serum electrolytes, glucose, Cr.
- Serum osmolality, urine osmolality.
- Urine Na⁺ (urine Na⁺ <10-20 mEq/L suggests volume depletion as the cause of hyponatremia).
- Assess for causes of SIADH (see Table 6).
- TSH, free T4, and cortisol levels.
- Consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. small cell lung cancer).
- Consider CT head if suspect CNS cause.

---

**Hypotonic**

- UNa<20 and FeNa >1% (renal losses).
  - CHF.
  - Cirrhosis and ascites.
  - Nephrotic syndrome.
  - Pregnancy.

**Hypertonic**

- UNa>20.
  - AKI, CKD.

**Iso-osmolar**

- Retention in ECF of large volumes of isotonic fluids that do not contain sodium (e.g. mannitol).
  - Pseudohyponatremia – lab artifact seen with severe hyperlipidemia or paraproteinemia (e.g. multiple myeloma).

**Hypovolemic**

- UNa>20.
  - Diuretics (especially thiazides).
  - Salt-wasting nephropathy.

**Hypervolemic**

- UNa<20 and FeNa >1% (renal losses).
  - CHF.
  - Cirrhosis and ascites.
  - Nephrotic syndrome.
  - Pregnancy.

**Euvolemic**

- Uosm>100.
  - SIADH (normal UNa).
  - Adrenal insufficiency.
  - Hypothyroidism.

- Uosm<100.
  - Psychogenic polydipsia.
  - Low solute – "tea & toast".

**Hyperosmolar (translocational)**

- Extra osmoles in ECF draw water out of cells diluting the Na⁺ in ECF.
- Usually glucose (rarely hypertonic mannitol).
- Every 10 mmol/L increase in blood glucose results in 3 mmol/L decrease in Na⁺.

**Central Pontine Myelinolysis**

- Cranial nerve palsies.
- Quadriplegia.
- Decreased LOC.

**Hypernatremia**

- Swollen cells.

**Hypoponatremia**

- Shrunken cells.
Treatment of Hyponatremia

• general measures for all patients
  1) treat underlying cause (e.g. restore ECF volume if volume depleted, remove offending drug, treat pain, nausea, etc.)
  2) restrict free water intake
  3) promote free water loss
  4) carefully monitor serum Na⁺, urine volume, and urine tonicity (e.g. high output of dilute urine may be a sign of impending rapid serum sodium correction)
  5) frequently ensure correction is not occurring too rapidly
    • monitor urine output frequently; high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia

A. Definitely Acute (known to have developed over <24-48 h)
• commonly occurs in hospital (dilute IV fluid, post-operative increased ADH)
• less risk from rapid correction since adaptation has not fully occurred
• if symptomatic
  • correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum [Na⁺] = 125-130 mEq/L
  • may need furosemide to address volume overload
• if asymptomatic, treatment depends on severity
  • if marked fall in plasma [Na⁺], treat as symptomatic

B. Chronic or Unknown
  1. if severe symptoms (seizures or decreased LOC)
     • must partially correct acutely
     • aim for increase of Na⁺ by 1-2 mEq/L/h for 4-6 h
     • limit total rise to 8 mEq/L in 24 h
     • IV 3% NaCl at 1-2 cc/kg/h
     • may need furosemide
  2. if asymptomatic
     • water restrict to <1 L/d fluid intake
     • consider IV 0.9% NS + furosemide (reduces urine osmolality, augments excretion of H₂O)
     • consider NaCl tablet
  3. refractory
     • furosemide and oral salt tablets
     • oral urea (osmotic aquaresis)
     • V2 receptor antagonists (e.g. tolvaptan)
  4. always pay attention to patient’s ECF volume status – if already volume-expanded, unlikely to give NaCl; if already volume-depleted, almost never appropriate to give furosemide

C. Options for Treatment of Overly-Rapid Correction
• give water (IV D5W)
• give ADH to stop water diuresis (DDAVP 1-2 µg IV)

Impact of IV Solution on Serum [Na⁺]
• formula to estimate the change in serum [Na⁺] caused by retention of 1 L of any infusate
  \[
  \text{TBW} = (\text{for men}) 0.6 \times \text{wt(kg)}; (\text{for women}) 0.5 \times \text{wt(kg)}
  \]

  \[
  \text{change in serum [Na⁺]} = \text{infusate [Na⁺]} - \text{serum [Na⁺]} \times \frac{1}{\text{TBW} + 1}
  \]

• formula assumes there are no losses of water or electrolytes

SYNDROME OF INAPPROPRIATE ANTI迪URETIC HORMONE SECRETION
1. urine that is inappropriately concentrated for the serum osmolality
2. high urine sodium (>20-40 mEq/L)
3. high FE₅₆
NP10 Nephrology Electrolyte Disorders Essential Med Notes 2015

Table 5. Disorders Associated with SIADH

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Pulmonary</th>
<th>CNS</th>
<th>Drugs</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell cancer</td>
<td>Pneumonia</td>
<td>Mass lesion</td>
<td>Antidepressants</td>
<td>Post-operative state</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Lung abscess</td>
<td>Encephalitis</td>
<td>TCAs</td>
<td>Pain</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>TB</td>
<td>Subarachnoid hemorrhage</td>
<td>SSRIs</td>
<td>Severe nausea</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>Acute respiratory failure</td>
<td>Stroke</td>
<td>Antineoplastics</td>
<td>HIV</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Asthma</td>
<td>Head trauma</td>
<td>Vincristine</td>
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<td></td>
<td>COPD</td>
<td>Acute psychosis</td>
<td>Cyclophosphamide</td>
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<td></td>
<td>Positive pressure ventilation</td>
<td>Acute intermittent porphyria</td>
<td>Anti-epileptics</td>
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<td></td>
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<td>Carbamazepine</td>
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<td>Leukemia</td>
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<td>Barbiturates</td>
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<td>Chlorpropamide</td>
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<td>ACEI</td>
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<td>Other</td>
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<td>DDAVP</td>
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<td>Oxytocin</td>
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<td></td>
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<td></td>
<td>Nicotine</td>
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</tr>
</tbody>
</table>

Hypernatremia

- hypernatremia: serum [Na⁺] >145 mEq/L
- too little water relative to total body Na⁺; always a hyperosmolar state
- usually due to NET water loss, rarely due to hypertonic Na⁺ gain
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

![Hypernatremia Diagram](image)

Signs and Symptoms
- with acute hypernatremia no time for adaptation, therefore more likely to be symptomatic
- adaptive response: cells import and generate new osmotically active particles to normalize size
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- ± polyuria, thirst, signs of hypovolemia

Complications
- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema due to ongoing brain hyperosmolality

Treatment of Hypernatremia
- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum Na⁺ frequently to ensure correction is not occurring too rapidly
  - if evidence of hemodynamic instability, must first correct volume depletion with NS bolus
  - loss of water is often accompanied by loss of Na⁺, but a proportionately larger water loss
  - use formula to calculate free water H₂O deficit and replace
  - encourage patient to drink pure water, as oral route is preferred for fluid administration
  - if unable to replace PO or NG, correct H₂O deficit with hypotonic IV solution (IV D5W, 0.45% NS [half normal saline], or 3.3% dextrose with 0.3% NaCl [“2/3 and 1/3”])
  - use formula (see Hyponatremia, NP8) to estimate expected change in serum Na⁺ with 1 L infusate
  - aim to to lower [Na⁺] by no more than 12 mEq/L in 24 h (0.5 mEq/L/h)
  - must also provide maintenance fluids and replace ongoing losses
- general rule: give 2 cc/kg/h of free water to correct serum [Na⁺] by about 0.5 mEq/L/h or 12 mEq/L/d

H₂O Deficit and TBW Equations
- TBW = 0.6 x wt (kg) men
- TBW = 0.5 x wt (kg) women
- \( H₂O \) deficit = TBW x ([Na⁺] plasma – 140) / 140

Correction of serum [Na⁺] in hypernatremia should not exceed 12 mEq/L/24 h

1 L D5W approximately equals 1 L of free water
1 L 0.45% NS approximately equals 500 mL of free water
DIABETES INSIPIDUS

- collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
- defect in central release of ADH (central DI) or renal response to ADH (nephrogenic DI)

Etiology

- central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
- nephrogenic DI: lithium (most common), hypokalemia, hypercalcemia, and congenital

Diagnosis

- urinary osmolality inappropriately low in patient with hypernatremia (U_{osm} < 300 mOsm/kg)
- serum vasopressin concentration may be absent, low (central), or elevated (nephrogenic)
- dehydration test: H2O deprivation until loss of 3% of body weight or until urinary osmolality rises above plasma osmolality; if urinary osmolality remains < 300 (fails to concentrate urine), most likely DI
- administer DDAVP (exogenous ADH) (10 µg intranasally or 2 µg SC or IV)
  - central DI: diagnosed if there is rise in urinary osmolality, fall in urine volume
  - treat with DDAVP
  - nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
  - treat with water (IV D5W or PO water), thiazides may help as well (reduced ECF volume stimulates proximal tubular reabsorption of sodium and water, leading to less delivery of glomerular filtrate to ADH sensitive parts of renal tubule, and therefore lower urine volume results)

Potassium Homeostasis

- Approximately 98% of total body K+ stores are intracellular
- Normal serum K+ ranges from 3.5-5.0 mEq/L
- In response to K+ load, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia
  - insulin, catecholamines, and acid-base status influence K+ movement into cells
    - aldosterone has a minor effect
  - Potassium excretion is regulated at the distal nephron
    - K+ excretion = urine flow rate x urine [K+]

Factors which Increase Renal K+ Loss

- hyperkalemia
- increased distal tubular urine flow rate and Na+ delivery (thiazides and loop diuretics)
- increased aldosterone activates epithelial sodium channel in cortical collecting duct, causing Na+ reabsorption and K+ excretion
- metabolic alkalosis
- hypomagnesemia
- increased non-reabsorbable anions in tubule lumen: HCO3–, penicillin, salicylate

Hypokalemia

- Serum [K+] < 3.5 mEq/L

Signs and Symptoms

- Usually asymptomatic, particularly when mild (3.0-3.5 mEq/L)
- N/V, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
- If severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
- Arrhythmias occur at variable levels of K+; more likely if digoxin use, hypomagnesemia, or CAD
- ECG changes are more predictive of clinical picture than serum [K+]
  - U waves most important (low amplitude wave following a T wave)
  - Flattened or inverted T waves
  - Depressed ST segment
  - Prolongation of Q-T interval
  - With severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity

Figure 6. ECG changes in hypokalemia
Approach to Hypokalemia
1. emergency measures: obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of K⁺ as cause of hypokalemia
3. assess contribution of dietary K⁺ intake
4. spot urine K:Cr (should be less than 1 in setting of hypokalemia)
   - if <1 consider GI loss
   - if >1 consider a renal loss
5. consider 24 h K⁺ excretion
6. if renal K⁺ loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum [Mg²⁺]

Figure 7. Approach to hypokalemia

Treatment
• treat underlying cause
• if true K⁺ deficit, potassium repletion (decrease in serum [K⁺] of 1 mEq is roughly 100-200 mEq of total body loss)
  - oral sources – food, tablets (K-Tab”), KCl liquid solutions; preferable route if the patient tolerates PO medications
  - IV – usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
  - max 40 mEq/L via peripheral vein, 60 mEq/L via central vein, max infusion 20 mEq/h
• K⁺-sparring diuretics (triamterene, spironolactone, amiloride) can prevent renal K⁺ loss
• restore Mg²⁺ if necessary
• if urine output and renal function are impaired, correct with extreme caution
• risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
• beware of excessive potassium repletion, especially if transcellular shift caused hypokalemia

Hyperkalemia
• serum [K⁺] >5.0 mEq/L

Signs and Symptoms
• usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
• impaired renal ammoniagenesis and metabolic acidosis
• ECG changes and cardiotoxicity (do not correlate well with serum [K⁺])
  - peaked and narrow T waves
  - decreased amplitude and eventual loss of P waves
  - prolonged PR interval
  - widening of QRS and eventual merging with T wave (sine-wave pattern)
  - AV block
  - ventricular fibrillation, asystole

**Figure 8. ECG changes in hyperkalemia**

**Table 6. Causes of Hyperkalemia**

<table>
<thead>
<tr>
<th>Factitious</th>
<th>Increased Intake</th>
<th>Transcellular Shift</th>
<th>Decreased Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample hemolysis*</td>
<td>Diet</td>
<td>Intravascular hemolysis</td>
<td>Decreased GFR</td>
</tr>
<tr>
<td>Sample taken from vein where IV KCl is running</td>
<td>KCl tabs</td>
<td>Rhabdomyolysis</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>Prolonged use of tourniquet</td>
<td>IV KCl</td>
<td>Tumor lysis syndrome</td>
<td>Low effective circulating volume</td>
</tr>
<tr>
<td>Leukocytosis (extreme)</td>
<td>Salt substitute</td>
<td>Insulin deficiency</td>
<td>• NSAIDs in renal insufficiency</td>
</tr>
<tr>
<td>Thrombocytosis (extreme)</td>
<td></td>
<td>Acidemia</td>
<td>Normal GFR but hypoaldosteronism</td>
</tr>
</tbody>
</table>

*Most common

**Table 7. Causes of Hyperkalemia with Normal GFR**

<table>
<thead>
<tr>
<th>Decreased Aldosterone Stimulus (low renin, low aldosterone)</th>
<th>Decreased Aldosterone Production (normal renin, low aldosterone)</th>
<th>Aldosterone Resistance (decreased tubular response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV</td>
<td>• Adrenal insufficiency of any cause (e.g. Addison’s disease, AIDS, metastatic cancer)</td>
<td>K⁺-sparing drugs</td>
</tr>
<tr>
<td></td>
<td>• ACEI</td>
<td>• Spironolactone</td>
</tr>
<tr>
<td></td>
<td>• ARBs</td>
<td>• Amiloride</td>
</tr>
<tr>
<td></td>
<td>• Heparin</td>
<td>• Triamterene</td>
</tr>
<tr>
<td></td>
<td>Congenital adrenal hyperplasia with 21-hydroxylase deficiency</td>
<td>Renal tubulo-interstitial disease</td>
</tr>
</tbody>
</table>

**Approach to Hyperkalemia**
1. emergency measures: obtain ECG, if life threatening begin treatment immediately
2. rule out factitious hyperkalemia; repeat blood test
3. hold exogenous K⁺ (PO and IV) and any K⁺ retaining medications
4. assess potential causes of transcellular shift
5. estimate GFR (calculate CrCl using Cockcroft-Gault)

**Treatment**
- acute therapy is warranted if ECG changes are present, or if patient is symptomatic
- tailor therapy to severity of increase in [K⁺] and ECG changes
  - [K⁺] <6.5 and normal ECG
    - treat underlying cause, stop K⁺ intake, increase the loss of K⁺ via urine and/or GI tract
  - [K⁺] between 6.5 and 7.0, no ECG changes: add insulin to above regimen
  - [K⁺] >7.0 and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

1. **Protect the Heart**
   - calcium gluconate 1-2 amps (10 mL of 10% solution) IV
   - antagonizes cardiac toxicity of hyperkalemia, protects cardiac conduction system, no effect on serum [K⁺]
   - onset within minutes, lasts 30-60 min (may require repeat doses during treatment course of hyperkalemia)
2. Shift $K^+$ into Cells

- regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
  - onset of action 15-30 min, lasts 1-2 h
  - monitor capillary blood glucose q1h because of risk of hypoglycemia
  - can repeat every 4-6 h
  - caution giving D50W before insulin if hyperkalemia is severe as it can cause a serious arrhythmia

- NaHCO$_3$, 1-3 ampules (given as 3 ampules of 7.5% or 8.4% NaHCO$_3$ in 1L D5W)
  - onset of action 15-30 min, transient effect, drives $K^+$ into cells in exchange for $H^+$
  - more effective if patient has metabolic acidosis

- $\beta_2$-agonist (Ventolin*) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  - onset of action 30-90 min, stimulates Na+/K+ ATPase
  - caution if patient has heart disease as may result in tachycardia

3. Enhance $K^+$ Removal from Body

- via urine (preferred approach)
  - furosemide ($\geq$40 mg IV), may need IV NS to avoid hypovolemia
  - fludrocortisone (synthetic mineralocorticoid) if suspect aldosterone deficiency

- via gastrointestinal tract
  - cation-exchange resins: calcium resinium or sodium polystyrene sulfonate (Kayexalate*)
    - increasingly falling out of favor due to risk of colonic necrosis; works by binding Na$^+$ in exchange for $K^+$, and controversial how much $K^+$ is actually removed
  - lactulose PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered – main benefit may be the diarrhea caused by lactulose)
  - Kayexalate* enemas with tap water

- dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

### Acid-Base Disorders

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic, and CNS function
- see Respiratory, R5 for more information on respiratory acidosis/alkalosis
- normal concentration of HCO$_3^-$ = 24 mEq/L (range: 22-30)
- normal $pCO_2$ = 40 mmHg (range: 36-44)
- each acid base disorder has an appropriate compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder (e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis)

#### Figure 9. Approach to acid-base disorders

**Approach**

1. **Identify the primary disturbance** (see Figure 8)
   - respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis
2. Evaluate compensation. If compensation is not appropriate, a second acid-base disorder is likely present
   - compensation occurs in the same direction as the primary disturbance
   - metabolic acidosis: for every 1 mEq/L decrease in HCO₃⁻, pCO₂ should decrease by 1 mmHg
   - metabolic alkalosis: for every 10 mEq/L increase in HCO₃⁻, pCO₂ should increase by 5-7 mmHg
   - respiratory acidosis: for every 10 mmHg increase in pCO₂, HCO₃⁻ should increase by 1 (acute) or 3 (chronic) mEq/L
   - respiratory alkalosis: for every 10 mmHg decrease in pCO₂, HCO₃⁻ should decrease by 2 (acute) or 5 (chronic) mEq/L

3. Calculate Plasma AG
   - AG = [Na⁺] - ([HCO₃⁻] + [Cl⁻])
   - baseline = 12, range 10-14 mEq/L
   - AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 mEq/L (e.g. if plasma [albumin]= 20 g/L, expect AG = 6 mEq/L)

4. If AG elevated, compare increase in AG with decrease in HCO₃⁻
   - if increase in AG < decrease in HCO₃⁻, there is a coexisting non-AG metabolic acidosis
   - if increase in AG > decrease HCO₃⁻, there is a coexisting metabolic alkalosis

5. Calculate Osmolar Gap
   - osmolar gap = measured osmolality – calculated osmolality
   - calculated osmolality = (2 x [Na⁺]) + [urea] + [glucose] (all units are in mEq/L)
   - normal osmolar gap <10
   - if AG >10, consider: methanol poisoning, ethylene glycol poisoning, or another cause of acidosis plus ethanol ingestion

## Metabolic Acidosis

### Etiology and Pathophysiology

1. Increased AG Metabolic Acidosis (4 types)
   a. L-lactic acid
      - Type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
      - Type B: non-hypoxic – multiple causes; the most common is failure to metabolize normally produced lactate in the liver due to severe liver disease; other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain antiretrovirals, large tumours, mitochondrial myopathies
      - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
      - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria metabolize carbohydrate load into D-lactic acid, diminished colonic motility and impaired D-lactate metabolism
   b. Ketoacidosis
      - diabetic
      - starvation
      - alcoholic (decreased carbohydrate intake and vomiting)
   c. Toxins
      - methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
      - ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
      - salicylate (e.g. ASA) overdose: causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacid (salicylate activates fat breakdown)
   d. Advanced renal failure (e.g. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)

2. Normal AG Metabolic Acidosis (Hyperchloremic Acidosis)
   - diarrhea (HCO₃⁻ loss from GI tract)
   - RTA
      - type I RTA (distal): inability to secrete H⁺ in collecting duct, leading to impaired excretion of ammonium into urine
      - type II RTA (proximal): impaired HCO₃⁻ reabsorption
      - type IV RTA: defective ammoniagenesis due to decreased aldosterone, hypo responsiveness or hyperkalemia

### Useful Equations

- **AG** = [Na⁺] - ([HCO₃⁻] + [Cl⁻])
- Normal range = 10-14 mEq/L
- Calculated serum osmolality = 2Na + BUN/2.8 + glucose/18

### Causes of Increased AG Metabolic Acidosis

- MUDPILES CAT
  - Methanol
  - Uremia
  - Diabetic ketoacidosis
  - Paraldehyde
  - Isopropyl alcohol/Iron/Ibuprofen/
  - Indomethacin
  - Lactic acidosis
  - Ethylene glycol
  - Salicylates
  - Cyanide and Carbon monoxide
  - Alcoholic ketoacidosis
  - Toluene
  - or
- **KARMEL**
  - Ketoacidosis
  - ASA
  - Renal failure
  - Methanol
  - Ethylene glycol
  - Lactic acidosis
Treatment of Metabolic Acidosis

- treat underlying cause
  - insulin for DKA
  - ethanol/fomepizole + dialysis for methanol or ethylene glycol poisoning
  - alkaline diuresis ± dialysis if ASA overdose

- correct coexisting disorders of K⁺ (see Hyperkalemia, NP12)

- consider treatment with exogenous alkali (e.g. NaHCO₃) if
  - severe reduction in [HCO₃⁻] e.g. <8 mEq/L, especially with very low pH (<7)
  - no metabolizable anion (e.g. salicylate, formate, oxalate, or sulphate); note that lactate and ketoacid anions can be metabolized to HCO₃⁻

- risks of sodium bicarbonate therapy
  - hypokalemia: causes K⁺ to shift into cells (correct K⁺ deficit first)
  - ECF volume overload: Na⁺ load given with NaHCO₃ can exacerbate pulmonary edema
  - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to HCO₃⁻, and persisting hyperventilation

Metabolic Alkalosis

Pathophysiology

- requires initiating event and maintenance factors
- precipitating factors
  - GI (vomiting, NG tube) or renal loss of H⁺
  - exogenous alkali (oral or parenteral administration), milk alkali syndrome
  - diuretics (contraction alkalosis): decreased excretion of HCO₃⁻, decreased ECF volume, therefore increased [HCO₃⁻]
  - post-hypercapnia: renal compensation for respiratory acidosis is HCO₃⁻ retention, rapid correction of respiratory disorder results in transient excess of HCO₃⁻

- maintenance factors
  - volume depletion: increased proximal reabsorption of NaHCO₃ and increased aldosterone
  - hyperaldosteronism (1º or 2º): distal Na⁺ reabsorption in exchange for K⁺ and H⁺ excretion leads to HCO₃⁻ generation; aldosterone also promotes hypokalemia
  - hypokalemia: transtubular K⁺/H⁺ exchange, stimulus for ammoniagenesis, and HCO₃⁻ generation

Evaluate Compensation (identify co-existing respiratory acid-base disorders)

- hypoventilation (an upper limit to compensation exists – breathing cannot be stopped)

Treatment

- treat underlying cause
- correct underlying disease, replenish K⁺ and Mg²⁺ deficits, and possibly K⁺-sparing diuretic
**Parenchymal Kidney Diseases**

## Vascular Diseases of the Kidney

### LARGE VESSEL DISEASE

<table>
<thead>
<tr>
<th>Large Vessel Disease</th>
<th>Small Vessel Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal artery occlusion (infarct)</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td>Renal artery stenosis (ischemia)</td>
<td>Atheroembolic renal disease</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
</tr>
<tr>
<td></td>
<td>Calcineurin inhibitor nephropathy</td>
</tr>
</tbody>
</table>

1. **RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)**
   - important, potentially reversible cause of renal failure

   **Etiology**
   - abdominal trauma, surgery, embolism, vasculitis, extra-renal compression, hypercoagulable state, aortic dissection
   - kidney transplant more vulnerable

   **Signs and Symptoms (depend on presence of collateral circulation)**
   - fever, N/V, flank pain
   - leukocytosis, elevated AST, ALP
   - marked elevated LDH (LDH >4x upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
   - acute onset HTN (activation of RAAS) or sudden worsening of long-standing HTN
   - renal dysfunction, e.g. elevated Cr (if bilateral, or solitary functioning kidney)

   **Investigations**
   - renal arteriography (more reliable but risk of atheroembolic renal disease)
   - contrast-enhanced CT or MR angiography, duplex Doppler studies (operator dependent)

   **Treatment**
   - prompt localization of occlusion and restoration of blood flow
   - anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
   - medical therapy in the long-term to reduce risk (e.g. antihypertensives)

2. **ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)**
   - chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
   - significant cause of ESRD: 15% in patients over 50 yr old (higher prevalence if significant vascular disease)
   - usually associated with large vessel disease elsewhere
   - causes of renal artery stenosis
     - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males >55 yr, smokers
     - electrolytes, osmolality (gently rehydrate when needed, e.g. CHF)
     - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset <30 yr) (gently rehydrate when needed, e.g. CHF)
   - when there is decreased RBF, GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the FF (GFR/RBF)
   - most common cause of secondary HTN (‘renovascular HTN’), 1-2% of all hypertensive patients
   - etiology
     - decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
     - increased angiotensin raises blood pressure in two ways
       1. causes generalized arteriolar constriction
       2. release of aldosterone increases Na⁺ and water retention
   - elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN
Risk Factors
- >50 yr old
- smoking
- other atherosclerotic disease (dyslipidemia, DM, diffuse atherosclerosis)

Signs and Symptoms
- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

Investigations
- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (e.g. captopril renal scan)
- renal arteriography (gold standard)

Treatment
- surgical: percutaneous angioplasty ± stent, surgical revascularization, occasionally surgical bypass
- medical: BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- little or no benefit if therapy is late (e.g. kidney is already shrunken), however, therapy can be considered to save the opposite kidney if normal

3. RENAL VEIN THROMBOSIS

Etiology
- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical presentation determined by rapidity of occlusion and formation of collateral circulation

Signs and Symptoms
- acute: N/V, flank pain, hematuria, elevated plasma LDH, ± rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria and/or tubule dysfunction

Investigations
- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

Treatment
- thrombolytic therapy ± percutaneous thrombectomy for acute renal vein thrombosis
- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

SMALL VESSEL DISEASE

1. HYPERTENSIVE NEPHROSCLEROSIS
- see Hypertension, NP31

2. ATHEROEMBOLIC RENAL DISEASE
- progressive renal insufficiency due to embolic obstruction of small- and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
- anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
- investigations
  - eosinophilia, eosinophiluria, and hypocomplementemia
  - renal biopsy: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small-/medium-sized vessels
- treatment
  - no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
- prognosis: poor overall, at least a third will develop ESRD
3. THROMBOTIC MICROANGIOPATHY
- etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
- treatment
  - depends on cause
  - supportive therapy
  - TTP-HUS: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)
- avoid platelet transfusions and ASA

4. CALCINEURIN INHIBITOR NEPHROPATHY
- cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplants (e.g. heart)
- acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
  - prerenal azotemia
  - treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunosuppressive drug
- chronic: result of obliterator arteriolopathy causing interstitial nephritis and CKD (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors

Glomerular Diseases

HISTOLOGICAL TERMS OF GLOMERULAR CHANGES

Extent of Changes
- terms used to describe histologically the number of glomeruli affected in a given condition
  - diffuse: majority of glomeruli abnormal
  - focal: some glomeruli affected
- terms used to describe histologically the extent to which individual glomeruli are affected in a given condition
  - global: entire glomerulus abnormal
  - segmental: only part of the glomerulus abnormal

Types of Changes
- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane
- crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration form crescent-shape in Bowman's space

CLINICAL PRESENTATION OF GLOMERULAR DISEASE

Important Points to Remember
- glomerular diseases have diverse clinical presentations including hematuria, proteinuria, HTN, edema, and decreased GFR
- each glomerulopathy presents as one of four major glomerular syndromes (these are NOT diagnoses)
  - asymptomatic urinary abnormalities
    - proteinuria
    - hematuria
  - nephritic syndrome
    - acute GN
    - rapidly progressive GN
  - nephrotic syndrome
  - ESRD
- glomerulopathies can be caused by a primary disease or can occur secondary to a systemic disease
- some glomerulopathies can present as more than one syndrome at different times

The Nephritic-Nephrotic Spectrum
- glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes
PROTEINURIA

- hallmark of nephrotic syndromes
- 24 h urine protein: gold standard to assess degree of proteinuria
  - microalbuminuria
    - defined as ACR ≥25 mg/g (female) or ACR ≥18 mg/g (male)
    - marker of vascular endothelial function
    - an important prognostic marker for kidney disease in DM and HTN (see *Diabetes*, NP28)
  - an elevated ACR ≥18 or 25 mg/g is the earliest sign of diabetic nephropathy
- composition of normal total urine protein
  - upper limit of normal daily excretion of total protein is 150 mg/d
  - upper limit of normal daily excretion of albumin is 30 mg/d
  - the other normally excreted proteins are either filtered low molecular weight proteins (such as immunoglobulin light chains or β-2 microglobulin) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)

Pathologic Proteinuria

Tubulointerstitial
- Normally low molecular weight proteins (< 60 kDa) pass through glomerular filtration barrier and are reabsorbed in proximal tubule
- Proximal tubule dysfunction causes impaired reabsorption and increased excretion of low molecular weight proteins
- Albumin (> 60 kDa) is not affected; thus, edema is partly secondary to salt and water retention

Glomerular
- Normally, the filtration barrier is selectively permeable to size (< 60 kDa) and charge (repels negative particles); thus, albumin is filtered to a very limited extent through a normal glomerulus
- Damage to any component of the glomerular filtration barrier results in loss of albumin and other high molecular weight proteins; thus, edema is secondary to hypoalbuminemia (low oncotic pressure), but also due to enhanced renal tubular reabsorption of filtered sodium and water (possibly due to filtered proteins stimulating the action of cortical collecting duct epithelial sodium channel)

Overflow
- Increased production of low molecular weight proteins which exceeds the reabsorptive capacity of the proximal tubule
- Plasma cell dyscrasias: produce light chain Ig (multiple myeloma, Waldenstrom’s macroglobulinemia, monoclonal gammopathy of undetermined significance)

Figure 11. Spectrum of glomerular pathology

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>Intermediate Proteinuria</th>
<th>Nephritic Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSGS</td>
<td>Membranoproliferative GN</td>
<td>Diffuse proliferative GN</td>
</tr>
<tr>
<td>Membranous glomerulopathy</td>
<td>Focal proliferative GN</td>
<td>Crescentic GN</td>
</tr>
<tr>
<td>Minimal change</td>
<td>IgA nephropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic membranoproliferative GN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV, HCV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SLE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinemia</td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Figure 12. Classification of proteinuria

Table 9. Daily Excretion of Protein

<table>
<thead>
<tr>
<th>Daily Excretion</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 mg total protein (and &lt; 30 mg albumin)</td>
<td>Normal</td>
</tr>
<tr>
<td>30-300 mg albumin</td>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>&gt;3500 mg total protein/1.73m² BSA</td>
<td>Nephrotic range proteinuria</td>
</tr>
<tr>
<td>Variable amount of proteinuria</td>
<td>Can be seen with glomerular disease; e.g. mild glomerular disease can lead to a mild degree of proteinuria, proliferative lesions may also be associated with some degree of proteinuria</td>
</tr>
<tr>
<td>Up to 2,000 mg per d</td>
<td>Possible tubular disease because of failure to reabsorb filtered proteins</td>
</tr>
</tbody>
</table>
**Investigations**
- urine R&M, C&S, urea, Cr
- further workup (if degree of proteinuria >0.5 g/d, casts, and/or hematuria)
  - CBC, glucose, electrolytes, 24 h urine protein, and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic U/S
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA (PR3), Hep B, Hep C, HIV, ASOT
- indications for nephrology referral
  - generally, if there is "heavy" (ACR >265 mg/g) proteinuria, should refer to nephrologist
  - definitely if there is nephrotic syndrome: marked proteinuria >3.5 g/1.73m²/d with hypoalbuminemia (<35 g/L)

**HEMATURIA**
- hallmark of nephritic syndromes
- presence of blood or RBCs in urine
  - gross hematuria: pink, red, or tea-colored urine
    - in gross hematuria, the urine should be centrifuged:
      - if the sediment is red, true hematuria
      - if the supernatant is red, test for heme with a dipstick
        - if supernatant positive for heme: myoglobinuria or hemoglobinuria
        - if negative for heme: pseudo-hematuria; consider medications (e.g. rifampin), food dyes (e.g. beets), or metabolites (e.g. porphyria)
  - microscopic hematuria: normal colored urine, >2-3 RBCs/HPF on microscopy

---

**Figure 13. Approach to red urine**

**Investigations for Hematuria**
- Hx and P/E: family history of nephrolithiasis, hearing loss (Alport’s), cerebral aneurysm (PCKD), diet, recent UTI, irritative and obstructive urinary symptoms (UTI)
- urine R&M, C&S, urea, Cr
- renal U/S
- 24 h urine stone workup if there is a history of stone formation or if there is a stone noted on imaging: calcium, oxalate, citrate, magnesium, uric acid, cysteine
- further workup (if casts and/or proteinuria): CBC, electrolytes, 24 h urine protein and Cr, serology (ANA, RF, C3, C4, p-ANCA, c-ANCA, ASOT)
- consider urology consult and possible cystoscopy if not clearly a nephrologic source for hematuria or if >50 yr of age
**Glomerular Syndromes**

1. **ASYMPTOMATIC URINARY ABNORMALITIES**

**Clinical/Lab Features**
- proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
  - isolated proteinuria
    - can be postural
    - occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
  - hematuria with or without proteinuria
    - IgA nephropathy (Berger's disease): most common type of primary glomerular disease worldwide, usually presents after viral URTI
    - hereditary nephritis (Alport’s disease): X-linked nephritis often associated with sensorineural hearing loss; proteinuria <2 g/d
    - thin basement membrane disease: usually autosomal dominant, without proteinuria; benign
    - benign recurrent hematuria: hematuria associated with febrile illness, exercise, or immunization; a diagnosis of exclusion after other possibilities are ruled out

2. **NEPHRITIC SYNDROME**

**ACUTE NEPHRITIC SYNDROME**
- a subset of nephritic syndrome in which the clinical course proceeds over days

**Etiology**
- etiology can be divided into low and normal complement levels (see Figure 14)
- frequently immune-mediated, with Ig and C3 deposits found in GBM
- outcome dependent on etiology

**Clinical/Lab Features**
- proteinuria (but <3.5 g/1.73 m²/d), abrupt onset hematuria (microscopic or macroscopic, azotemia (increased Cr and urea), RBC casts and/or dysmorphic RBCs in urine, oliguria, HTN (due to salt and water retention), peripheral edema/puffy eyes, smoky urine

---

**Figure 14. Approach to nephritic syndrome**

**RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS/CRESCENTIC GLOMERULONEPHRITIS**
- a subset of nephritic syndrome in which the clinical course proceeds over weeks to months
- clinical diagnosis, not histopathological
- any cause of GN can present as RPGN (except minimal change disease)
- additional etiologies seen only as RPGN: Goodpasture’s syndrome and granulomatosis with polyangiitis (previously called Wegener’s granulomatosis)

---

**Features of Nephritic Syndrome**

**PHAROH**
- Proteinuria
- Hematuria
- Azotemia
- RBC casts
- Oliguria
- Hypertension

IgA nephropathy is the most common type of primary glomerular disease worldwide.
Clinical/Lab Features
• fibrous crescents typically present on renal histopathology
• RBC casts and/or dysmorphic RBCs in urine
• classified by immunofluorescence staining
  • Type I: Anti-GBM mediated (15% of cases)
  • Type II: Immune Complex Mediated (24% of cases)
  • Type III: Non-Immune Mediated (60% of cases)
  • Type IV: Double Antibody Positive
• treatment: underlying cause for postinfectious; corticosteroids + cyclophosphamide or other cytotoxic agent + plasmaphoresis in select cases
• prognosis: 50% recovery with early treatment, depends on underlying cause

3. NEPHROTIC SYNDROME

Clinical/Lab Features
• heavy proteinuria (>3.5 g/1.73m²/d)
• hypoalbuminemia
• edema
• hyperlipidemia (elevated LDL cholesterol), lipiduria (fatty casts and oval fat bodies on microscopy)
• hypercoagulable state (due to antithrombin III, Protein C, and Protein S urinary losses)
• patient may report frothy urine
• glomerular pathology on renal biopsy
  ▪ minimal change disease (or minimal lesion disease or nil disease) – e.g. glomeruli appear normal on light microscopy
  ▪ membranous glomerulopathy
  ▪ focal segmental glomerulosclerosis (FSGS)
  ▪ membranoproliferative GN
  ▪ nodular glomerulosclerosis
• each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause proteinuria without obvious glomerular pathology)

Table 10. Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Secondary Causes</th>
<th>Minimal Change</th>
<th>Membranous Glomerulopathy</th>
<th>Focal Segmental Glomerulosclerosis</th>
<th>Membranoproliferative Glomerulonephritis</th>
<th>Nodular Glomerulosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>HBV, SLE, solid tumors (lung, breast, GI)</td>
<td>Reflux nephropathy, HIV, HBV, obesity</td>
<td>HCV, malaria, SLE, leukemia, lymphoma, infected shunt</td>
<td>DM, amyloidosis</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Causes</th>
<th>Therapy</th>
<th>Therapy</th>
<th>Therapy</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Steroids</td>
<td>Reduce BP, ACEI, steroids</td>
<td>Steroids, ACEI/ARB for proteinuria</td>
<td>Aspirin®, ACEI, dipyridamole (Persantine®) – controversial</td>
</tr>
<tr>
<td>Gold, penicillamine</td>
<td>Heroin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. END STAGE RENAL DISEASE
• refer to section End Stage Renal Disease, NP35

INVESTIGATIONS FOR GLOMERULAR DISEASE
• blood work
  ▪ first presentation: electrolytes, Cr, urea, albumin, fasting lipids
  ▪ determining etiology: CIC, ESR, serum immunoelectrophoresis, anti-GBM, C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV
• urinalysis: RBCs, WBCs, casts, protein
• 24 h urine for protein and CrCl
• radiology
  ▪ CXR (infiltrates, CHF, pleural effusion)
  ▪ renal U/S
• renal biopsy (percutaneous or open) if heavy proteinuria or renal insufficiency and cause is not obviously diabetic nephropathy
• urine immunoelectrophoresis
  ▪ for Bence-Jones protein if proteinuria present

SECONDARY CAUSES OF GLOMERULAR DISEASE

Amyloidosis
• nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
• presents as nephrotic range proteinuria with progressive renal insufficiency
• can be primary or secondary
• secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy
Systemic Lupus Erythematosus

- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- GN caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis

Henoch-Schönlein Purpura

- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia, and fever
- glomeruli show varying degrees of mesangial hypercellularity
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

Goodpasture’s Disease

- antibodies against type IV collagen present in lungs and GBM
- more common in 3rd and 6th decades of life, males slightly more affected than females
- present with RPGN type I and hemoptysis/dyspnea
- pulmonary hemorrhage more common in smokers and males
- treat with plasma exchange, cyclophosphamide, prednisone

ANCA-Associated Vasculitis (e.g. Granulomatosis with Polyangiitis and Microscopic Polyangiitis [formerly Wegener’s Granulomatosis])

- PR3-ANCA (c-ANCA) most commonly associated with the clinical picture of granulomatosis with polyangiitis (previously called Wegener’s granulomatosis)
- MPO-ANCA (p-ANCA) most commonly associated with the clinical picture of microscopic polyangiitis
- renal involvement very common
- focal segmental necrotizing RPGN with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treating typically involves cyclophosphamide and prednisone

Cryoglobulinemia

- cryoglobulins: monoclonal IgM and polyclonal IgG
- presents as purpura, fever, Raynaud’s phenomenon, and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

Shunt Nephritis

- immune-complex mediated nephritis associated with chronically infected ventriculostrial shunts inserted for treatment of hydrocephalus
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients
HIV-Associated Renal Disease
1. direct nephrotoxic effect of HIV infection, antiretroviral drugs (e.g. tenofovir, indinavir), and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy
   ▪ histology: focal and segmental glomerular collapse with mesangial sclerosis; “collapsing FSGS”
   ▪ tubular cystic dilation and tubulo-reticular inclusions
   ▪ clinical features: predominant in African American men, heavy proteinuria, progressive renal insufficiency
   ▪ prognosis: kidney failure within 1 yr without treatment
   ▪ therapy: short-term, high dose steroids, ACEI, HAART

Infective Endocarditis
- manifests as mild form of acute nephritic syndrome with decreased serum complement
- S. aureus is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

Hepatitis B
- can result in membranous nephropathy, polyarteritis nodosa, membranoproliferative GN

Hepatitis C
- can result in membranoproliferative GN, cryoglobulinemia, and membranous nephropathy

Syphilis
- can result in membranous GN

Tubulointerstitial Disease

TUBULOINTERSTITIAL NEPHRITIS

Definition
- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

Signs and Symptoms
- manifestation of disease depends on site of tubule affected
  1. proximal tubule (e.g. multiple myeloma, heavy metals)
     ▪ Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hypouricemia
     ▪ proximal RTA (decreased bicarbonate absorption): Type II RTA
  2. distal tubule (e.g. amyloidosis, obstruction)
     ▪ distal RTA (Type I RTA), usually hypokalemic
     ▪ Na⁺-wasting nephropathy
     ▪ ± hyperkalemia leading to type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
  3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
     ▪ urinary concentrating defect leading to mild nephrogenic DI
     ▪ polyuria

1. ACUTE TUBULOINTERSTITIAL NEPHRITIS

Definition
- rapid (days to weeks) decline in renal function
- 10-20% of all AKI

Etiology
- hypersensitivity
  1. antibiotics: β-lactams, sulfonamides, rifampin, quinolones, cephalosporins
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
- infections
  ▪ bacterial pyelonephritis, Streptococcus, brucellosis, Legionella, CMV, EBV, toxoplasmosis, leptospirosis
- immune
  ▪ SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia
  ▪ idiopathic

Pathophysiology
- acute inflammatory cell infiltrates into renal interstitium
**Signs and Symptoms**
- AKI
- if hypersensitivity reaction: may see fever, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
- if pyelonephritis: flank pain and costovertebral angle (CVA) tenderness
- other signs and symptoms based on underlying etiology
- HTN and edema are uncommon

**Investigations**
- mild, non-nephrotic range proteinuria and microscopic hematuria
- urine
  - sterile pyuria, WBC casts, mild proteinuria, hematuria
  - eosinophils if AIN
- blood work
  - increased Cr and urea
  - eosinophilia if drug reaction
  - normal AG metabolic acidosis (RTA)
  - hypophosphatemia, hyperkalemia, hyponatremia
- gallium scan often shows intense signal due to inflammatory infiltrate
- renal biopsy definitive

**Treatment**
- treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

**Prognosis**
- recovery within 2 wk if underlying insult can be eliminated
- the longer the patient is in renal failure, the less likely full renal recovery becomes

2. **CHRONIC TUBULOINTERSTITIAL NEPHRITIS**

**Definition**
- characterized by slowly progressive renal failure, moderate proteinuria, and signs of abnormal tubule function

**Etiology**
- persistence or progression of acute TIN
- urinary tract obstruction: most important cause of chronic TIN (tumors, stones, bladder outlet obstruction, vesicoureteral reflux)
- chronic pyelonephritis due to vesicoureteral reflux or UTI with obstruction
- nephrotoxins
  - exogenous
    - analgesics: NSAIDs (common), acetaminophen
    - cisplatin, lithium, cyclosporine, tacrolimus
    - heavy metals (lead, cadmium, copper, lithium, mercury, arsenic)
    - radiation
  - Chinese herbs
  - endogenous
    - hypercalcemia, hypokalemia, oxalate, uric acid nephropathy
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma, lymphoma
- granulomatous: TB, sarcoidosis, granulomatosis with polyangitis
- immune: SLE, Sjögren’s, cryoglobulinemia, Goodpasture’s, amyloidosis, renal graft rejection, vasculitis
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

**Pathophysiology**
- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

**Signs and Symptoms**
- tubular dysfunction (e.g. acidosis, electrolyte disturbances)
- progressive renal failure with azotemia and uremia
- dependent on underlying etiology

**Treatment**
- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders ($\text{Ca}^{2+}$, $\text{PO}_4^{3-}$) and anemia
Findings which Suggest Chronic Tubulointerstitial Nephritis
- normal AG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi’s syndrome
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- U/S: shrunken kidneys with irregular contours

3. ACUTE TUBULAR NECROSIS

Definition
- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

Etiology

Clinical Presentation
- typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
- urine: high FE Na+, pigmented-granular casts

Complications
- hyperkalemia: can occur rapidly and cause serious arrhythmias
- metabolic acidosis, decreased Ca²⁺, increased PO₄³⁻, hypoalbuminemia

Investigations
- blood work: CBC, electrolytes, Cr, urea, Ca²⁺, PO₄³⁻, blood gases
- urine: R&N, electrolytes, osmolality, microscopic urinalysis searching for pigmented granular casts
- ECG
- abdominal U/S
- rule out other causes of prerenal/postrenal azotemia and intrinsic AKI (GN, AIN, vasculitis)

Therapy
- largely supportive once underlying problem is corrected
- loop diuretics may help manage volume overload and reduce tubular metabolic requirements to allow for recovery (controversial)
- consider early dialysis in severe/rapidly progressing cases to prevent uremic syndrome

Prevention
- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast
  - give N-acetylcysteine 600-1200 mg PO bid day before and day of procedure, give intravenous isotonic fluid (either NaCl or NaHCO₃)
  - isotonic NaHCO₃ at 3 mL/kg over 1 h before procedure and 1 mL/kg/h for 6 h post-procedure if not contraindicated
  - avoid giving diuretics, ACEI, cyclosporine on morning of procedure if possible
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency

Meta-Analysis: Effectiveness of Drugs for Preventing Contrast-Induced Nephropathy


Purpose: To determine the effectiveness of N-acetylcysteine, theophylline, fenoldopam, dopamine, Agarist, statins, furosemide, or mannitol on preventing nephropathy.

Study Selection: Only randomized, controlled trials that used these agents in patients receiving iodinated contrast.

Results: In the 41 RCTs included N-acetylcysteine (RR = 0.62 [0.44-0.88]) and theophylline (RR = 0.49 [0.23-1.08]) reduced the risk of nephropathy more than saline alone. Furosemide increased the risk (RR = 3.27 [1.48-7.26]). Other agents did not affect risk of nephropathy.

Conclusion: N-acetylcysteine is more renoprotective than hydration alone.
Analgesic Nephropathies

1. Vasomotor AKI
- normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
- NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
- more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
- clinically: develop prerenal azotemia within a few days of starting NSAID
- treatment: discontinue NSAID, dialysis rarely needed

2. Acute Interstitial Nephritis
- fenoprofen (60%), ibuprofen, naproxen
- may be associated with minimal change glomerulopathy and nephrotic range proteinuria
- resolves eventually with discontinuation of NSAID, may require interval dialysis
- short-term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

3. Chronic Interstitial Nephritis
- due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
- seen in patients who also have emotional stress, psychiatric symptoms, and GI disturbance
- papillary necrosis
  - gross hematuria, flank pain, declining renal function
  - calyceal filling defect seen with IVP – “ring sign”
- increased risk of transitional cell carcinoma of renal pelvis
- good prognosis if discontinue analgesics

4. Acute Tubular Necrosis
- can be caused by acetaminophen
- incidence of renal dysfunction is related to the severity of acetaminophen ingestion
- vascular endothelial damage can also occur
- both direct toxicity and ischemia contribute to the tubular damage
- renal function spontaneously returns to baseline within 1-4 wk
- dialysis may be required during the acute episode of ingestion

5. Other Effects of NSAIDs
- sodium retention (2° to reduced GFR)
- hyperkalemia, HTN (2° to hyporeninemic hypoaldosteronism)
- excess water retention (due to elimination of ADH – antagonistic effect of prostaglandins)

Systemic Disease with Renal Manifestation

Diabetes
- diabetic nephropathy: presence of microalbuminuria or overt nephropathy (e.g. macroalbuminuria) in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 35-50% of patients with type 1 DM will develop nephropathy, unknown percentage of type 2
- at diagnosis up to 30% of patients with type 2 DM have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once macroalbuminuria is established, renal function declines, 50% patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially type 1 DM) and/or neuropathy (especially type 2 DM)
- indication of possible non-diabetic cause of renal disease in patients with DM:
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of systemic disease
  - inappropriate time course; rapidly rising Cr; renal disease in a patient with short duration of DM
  - family history of non-diabetic renal disease (e.g. PCKD, Alport’s)

DM is one of the causes of ESRD that does not result in small kidneys at presentation of ESRD. The others are amyloidosis, HIV nephropathy, PCKD, and multiple myeloma

ACEI can cause hyperkalemia. Therefore, be sure to watch serum K⁺, especially if patient has DM and renal insufficiency
NP29 Nephrology Systemic Disease with Renal Manifestation

DIABETIC RENAL COMPLICATIONS

1. Progressive Glomerulosclerosis
   • classic diabetic glomerular lesion: Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
   • more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix

2. Accelerated Atherosclerosis
   • common finding
   • decreased GFR
   • may increase angiotensin II production resulting in increased BP
   • increased risk of ATN secondary to contrast media

3. Autonomic Neuropathy
   • affects bladder leading to functional obstruction and urinary retention
   • residual urine promotes infection
   • obstructive nephropathy

4. Papillary Necrosis
   • type 1 DM susceptible to ischemic necrosis of medullary papillae
   • sloughed papillae may obstruct ureter
   • can present as renal colic or with obstructive features ± hydronephrosis

2013 Canadian Diabetes Association Clinical Practice Guidelines on Chronic Kidney Disease in Diabetes

- screen for microalbuminuria with a random urine test for albumin to Cr ratio (ACR) and eGFR with a serum Cr (e.g. using MDRD equation)
  - type 1 DM: annually in post-pubertal individuals after 5 yr of diagnosis
  - type 2 DM: at diagnosis, then annually
  - if eGFR >60 mL/min or ACR <2.0 mg/mEq; there is no CKD, re-screen in 1 yr
  - if urine ACR >20.0 mg/mEq: diagnose CKD
  - if ACR <20.0 mg/mEq but >2.0 mg/mEq: order serum Cr for eGFR in 3 mo and 2 repeats of random urine ACRs over the next 3 mo; if eGFR ≤60 mL/min or if >2/3 ACRs are >2.0 mg/mEq: diagnose CKD
  - if CKD diagnosed, ordered urine R + M and dipstick, if negative then diagnose CKD in DM
  - with CKD in DM: urine ACR and serum Cr (for eGFR) every 6 mo
  - delay screening if transient cause of albuminuria or low eGFR
  - evaluate for other causes of proteinuria, rule out non-diabetic renal disease
  - avoid unnecessary potential nephrotoxins (NSAIDs, aminoglycosides, dye studies)

Priorities in the Management of Patients with DM

1. vascular protection for all patients with DM
   • ACEI, antplatelet therapy (as indicated)
   • BP control, glycemic control, lifestyle modification, lipid control
2. optimization of BP in patients who are hypertensive
   • treat according to HTN guidelines
3. renal protection for DM patients with nephropathy (even in absence of HTN)
   • type 1 DM: ACEI
   • type 2 DM: CrCl >60 mL/min: ACEI or ARB – CrCl <60 mL/min: ARB
   • 2nd line agents: nondihydropyridine calcium channel blockers (diltiazem, verapamil)
   • ACEI and ARB can be safely used together if needed for control of significant proteinuria
     (monitor for hyperkalemia and acute rise in Cr)
   • check serum Cr and K⁺ levels within 1 wk of initiating ACEI or ARB and at time of acute illness
   • serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually
     stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
   • if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
   • consider holding ACEI, ARB, and/or diuretic with acute illness and in women before becoming pregnant
   • consider referral to nephrologist if ACR >60 mg/mEq, eGFR <30 mL/min, progressive kidney
     function loss, unable to achieve BP targets, or unable to stay on ACEI or ARB

Table 11. Stages of Diabetic Progressive Glomerulosclerosis

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ GFR (120-150%)</td>
<td>Detectable microalbuminuria (0-300 mg/24 h)</td>
<td>Macroalbuminuria (&gt;300 mg/24 h)</td>
<td>↑ proteinuria (&gt;600 mg/24 h)</td>
</tr>
<tr>
<td>– compensatory hyperfiltration</td>
<td>Albumin-Cr ratio (ACR) 2.0-20 mg/mEq in men (18-180 mg/dl), ACR 2.0-28 mg/mEq in women (25-250 mg/dl)</td>
<td>ACR in men &gt;20 mg/mEq, (180 mg/d)</td>
<td>↓ GFR</td>
</tr>
<tr>
<td>± slightly increased mesangial matrix</td>
<td>↑ mesangial matrix</td>
<td>ACR in women &gt;28 mg/mEq, (&gt;250 mg/d)</td>
<td>&lt;20% glomerular filtration surface area present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Proteinuria (+ ve urine dipstick)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal GFR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ ↑ ↑ mesangial matrix</td>
<td></td>
</tr>
</tbody>
</table>

Figure 17. GFR and urine protein over time in DM

Renoprotective Effect of Angiotensin-Receptor Antagonist Ibrahimation in Patients with Nephropathy Due to Type 2 DM

- Study: Multicenter, RCT, mean follow-up of 2.6 yr.
- Patients: 806 patients (mean age 70 yr) with type 2 DM, HTN, and nephropathy (24 h proteinuria >100 mg, serum Cr 88-285 µmol/L, [male], serum Cr 106-285 µmol/L, [female]).
- Intervention: BP control with irbesartan vs. amlodipine or placebo, with use of adjuncts (not including ACEI, ARBs, or CCI) as needed.
- Outcomes: Primary composite endpoint included doubling of serum Cr, ESRD, or death. Secondary composite endpoint included mortality and mortality or from cardiovascular death.
- Results: BP control was similar in all three arms. Irbesartan had a relative risk reduction of 20% vs. placebo and 23% vs. amlodipine for the primary end point. The irbesartan group had a 33% risk reduction vs. placebo and 37% reduction vs. amlodipine for risk of doubling serum Cr. Serum Cr increased more slowly in the irbesartan group vs. placebo or amlodipine. No difference in absolute mortality or secondary end point.
- Conclusion: Irbesartan conferred significant renoprotective benefits in patients with type 2 DM and nephropathy, independent of blood pressure lowering effects.
Scleroderma

- 50% of scleroderma patients have renal involvement (mild proteinuria, high Cr, HTN)
- histology: media thickened, "onion skin" hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
- 10-15% scleroderma patients have a "scleroderma renal crisis" (occurs in first few years of disease): malignant HTN, ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- renal involvement usually occurs early in the course of illness
- treatment: BP control with ACEI slows progression of renal disease

Multiple Myeloma

- see Hematology: H49
- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms
  - hypercalcemia
  - light chain cast nephropathy (LCCN, see below) or "myeloma kidney"
  - hyperuricemia
  - infection
  - secondary amyloidosis
  - monoclonal Ig deposition disease (MIDD)
  - diffuse tubular obstruction
- LCCN
  - large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
- proteinuria and renal insufficiency, can progress rapidly to kidney failure
- MIDD
  - deposits of monoclonal Ig in kidney, liver, heart, and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
- lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
- poor candidates for kidney transplantation

Malignancy

- cancer can have many different renal manifestations
- kidney transplantation cannot be performed unless malignancy is cured
  - solid tumors: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin's) or membranous GN (non-Hodgkin's)
  - renal cell carcinoma
  - tumor lysis syndrome: hyperuricemia, diffuse tubular obstruction
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumors/mets: postrenal failure secondary to obstruction
  - 2’ amyloidosis
  - radiotherapy (radiation nephritis)

Hypertension

- HTN occurs in about 20% of population
- etiology classified as primary ("essential"); makes up 90% of cases) or secondary
- primary HTN can cause kidney disease (hypertensive nephrosclerosis), which may in turn exacerbate the HTN
- secondary HTN can be caused by renal parenchymal or renal vascular disease
Hypertensive Nephrosclerosis

Table 12. Chronic vs. Malignant Nephrosclerosis

<table>
<thead>
<tr>
<th></th>
<th>Chronic Nephrosclerosis</th>
<th>Malignant Nephrosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles</td>
<td>Fibrinoid necrosis of arterioles, disruption of vascular endothelium</td>
</tr>
<tr>
<td><strong>Clinical Picture</strong></td>
<td>African American, underlying CKD, chronic hypertensive disease</td>
<td>Acute elevation in BP (dBP &gt;120 mmHg) HTN encephalopathy</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>Mild proteinuria, normal urine sediment</td>
<td>Proteinuria and hematuria (RBC casts)</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Blood pressure control, (target &lt;140/90) with frequent follow-up</td>
<td>Lower dBP to 100-110 mmHg within 6-24 h More aggressive treatment can cause ischemic event Identify and treat underlying cause of HTN</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Can progress to renal failure despite patient adherence</td>
<td>Lower survival if renal insufficiency develops</td>
</tr>
</tbody>
</table>

Renovascular Hypertension

- see Vascular Diseases of the Kidney, NP17

Renal Parenchymal Hypertension

- HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
- mechanism of HTN not fully understood but may include
  - excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  - production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  - ineffective sodium excretion with fluid overload

Investigations

- as well as investigations for renovascular HTN, additional tests may include
  - 24 h urinary estimations of Cr clearance and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy

Treatment

- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na+ restriction (88 mEq/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor K+ and Cr) if there is significant proteinuria (>300 mg/d)

Cystic Diseases of the Kidney

- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population over 50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive), and acquired cystic kidney disease (in chronic hemodialysis patients)

Adult Polycystic Kidney Disease

- autosomal dominant; at least 2 genes: PKD1 (chr 16p) and PKD2 (chr 4q)
- PKD1 (1:400), PKD2 (1:1,000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant polycystin gene but accumulate a series of second ‘somatic hits’ precipitating the condition
- PKD1 encodes a protein that is responsible for cell-cell and cell-matrix interaction and sensing fluid flow by associating with cilia
- PKD2 encodes a protein that is a Ca2+ permeable nonselective cation channel that associates with cilia and is thought to control intracellular Ca2+ in response to flow
- defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth
- extrarenal manifestations: most common; multiple asymptomatic hepatic cysts (33%), cerebral aneurysm (10%), diverticulosis, and mitral valve prolapse (25%)
- polycystic liver disease rarely causes liver failure
- less common: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta

Hypercalceemia complicates many cancers and can cause multiple kinds of renal disorders (renal vasoconstriction with reduced OTR, salt-wasting with volume depletion, risk of calcium kidney stones)
Signs and Symptoms
- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain
- hematuria (microscopic frequently initial sign, gross)
- nocturia (urinary concentrating defect)
- rarely extra-renal presentation (e.g. ruptured berry aneurysm, diverticulitis)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- ± palpable kidneys

Common Complications
- urinary tract and cyst infections, HTN, CRF, nephrolithiasis (5-15%), flank and chronic back pain

Clinical Course
- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10x normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

Investigations
- radiographic diagnosis: best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- gene linkage analysis for PKD1 for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)

Treatment
- goal: to preserve renal function by prevention and treatment of complications
- educate patient and family about disease, its manifestations, and inheritance pattern
- genetic counseling: transmission rate 50% from affected parent
- prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
- TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
- adequate hydration to prevent stone formation
- avoid contact sports due to greater risk of injury to enlarged kidneys
- screen for cerebral aneurysms if family history of aneurysmal hemorrhages
- monitor blood pressure and treat HTN with ACEI
- dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
- may require nephrectomy to create room for renal transplant

Medullary Sponge Kidney
- common, autosomal dominant, usually diagnosed in 4th-5th decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria, and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney
- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP leading to characteristic radial pattern (“bouquet of flowers”), “Swiss cheese” appearance on histological cross-section
- treat UTIs and stone formation as indicated
- does not result in renal failure

Autosomal Recessive Polycystic Kidney Disease
- 1:20,000 incidence
- prenatal diagnosis by enlarged kidneys
- perinatal death from respiratory failure
- patients who survive perinatal period develop CHF, HTN, CKD
- treated with kidney and/or liver transplant
Acute Kidney Injury

Definition
• abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
• formerly known as Acute Renal Failure

Clinical Features
• azotemia (increased BUN, Cr)
• abnormal urine volume: formally <0.5 ml/kg/h for >6 h but can manifest as anuria, oliguria, or polyuria

Investigations
• blood work: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), Ca²⁺, PO₄³⁻
• urine volume, C&S, R&M: sediment, casts, crystals
• urinary indices: electrolytes, osmolality
• fluid challenge (e.g. fluid bolus to rule out most prerenal causes)
• imaging: abdo U/S (assess kidney size, hydronephrosis, postrenal obstruction)
• indications for renal biopsy
  • diagnosis is not certain
  • prerenal azotemia or ATN is unlikely
  • oliguria persists >4 wk

Treatment
1. preliminary measures
  • prerenal
    • correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEI/ARB (gently rehydrate when needed, e.g. CHF)
  • renal
    • address reversible renal causes: discontinue nephrotoxic drugs, treat infection, and optimize electrolytes
  • postrenal
    • consider obstruction: structural (stones, strictures) vs. functional (neuropathy)
    • treat with Foley catheter, indwelling bladder catheter, nephrostomy, stenting
2. treat complications
  • fluid overload
  • NaCl restriction
  • high dose loop diuretics
  • hyperkalemia (refer to Approach to Hyperkalemia, NP12)

Approach to AKI

Differentiating Prerenal from ATN

<table>
<thead>
<tr>
<th>Prerenal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis</td>
<td>Normal</td>
</tr>
<tr>
<td>Urine [Na⁺]</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Urine [Na⁺]/[Cr]</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>&gt; 500</td>
</tr>
<tr>
<td>FeNa</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

Drugs Implicated in Prerenal Azotemia
• Diuretics
• NSAIDs
• ACEI/ARBs

Indications for Dialysis (refractory to medical therapy)
AE IOU
Acidosis
Electrolyte imbalance (K⁺)
Intoxication
Overload (fluid)
Uromic encephalopathy, pericarditis, urea > 35-50 mM

Figure 18. Approach to AKI

The 2 most common causes of acute kidney injury in hospitalized patients are prerenal azotemia and ATN; remember that prerenal failure can lead to ATN

Clues to Renal Etiology
• Appropriate clinical context
• Urinalysis positive for casts:
  • Pigmented granular – ATN
  • WBC – AIN
  • RBC – GN

Clues to Postrenal Etiology
• Known solitary kidney
• Older man
• Recent retroperitoneal surgery
• Anuria
• Palpable bladder
• U/S shows hydronephrosis

The 2 most common causes of acute kidney injury in hospitalized patients are prerenal azotemia and ATN; remember that prerenal failure can lead to ATN

Clues to Prerenal Etiology
• Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
• Increased [urea] >> Increased [Cr]
• Urine osmolality >500 mOsm/kg
• Fractional excretion of Na⁺ < 1%
- adjust dosages of medications cleared by kidney (e.g. amiodarone, digoxin, ciclosporin, tacrolimus, some antibiotics, and chemotherapeutic agents)
- dialysis

3. definitive therapy depends on etiology
- note: renal transplant is not a therapy for AKI

**Prognosis**
- high morbidity and mortality in patients with sustained AKI and multi-organ failure

## Chronic Kidney Disease

### Definition
- progressive and irreversible loss of kidney function
- abnormal markers (Cr, urea)
  - GFR <60 mL/min for >3 mo; or
  - kidney pathology seen on biopsy; or
  - decreased renal size on U/S (kidneys <9 cm)
- clinical features of CKD
  - volume overload and HTN
  - electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
  - uremia

### Incidence of Etiologies of CKD

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>42.9%</td>
</tr>
<tr>
<td>HTN</td>
<td>26.4%</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>9.9%</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>7.7%</td>
</tr>
<tr>
<td>Interstitial nephritis/Pyelonephritis</td>
<td>4.0%</td>
</tr>
<tr>
<td>Cystic/Hereditary/Congenital</td>
<td>3.1%</td>
</tr>
<tr>
<td>Secondary GN/Vasculitis</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

### Prognosis
- high morbidity and mortality in patients with sustained AKI and multi-organ failure

### Table 13. Stages of CKD (KDIGO, 2013)

<table>
<thead>
<tr>
<th>GFR categories (mL/min/1.73m²)</th>
<th>Persistent Albuminuria Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td>G1 ≥90</td>
<td>1 if CKD</td>
</tr>
<tr>
<td>G2 60-89</td>
<td>1 if CKD</td>
</tr>
<tr>
<td>G3a 45-59</td>
<td>1</td>
</tr>
<tr>
<td>G3b 30-44</td>
<td>2</td>
</tr>
<tr>
<td>G4 15-29</td>
<td>3</td>
</tr>
<tr>
<td>G5 &lt;15 (kidney failure)</td>
<td>4+</td>
</tr>
</tbody>
</table>

The numbers in the boxes are a reflection of the risk of progression and are a guide to the frequency of monitoring/year

“D” is added to G5 for patients requiring dialysis

Classification is based on cause, GFR, and amount of albuminuria

Rate of progression and risk of complications are determined by the cause of CKD

### Management of Chronic Kidney Disease

- **diet**
  - preventing HTN and volume overload
  - Na+ and water restriction
  - preventing electrolyte imbalances
  - K+ restriction (40 mEq/d)
  - PO₄³⁻ restriction (1 g/d)
  - avoid extra-dietary Mg²⁺ (e.g. antacids)
  - preventing uremia and potentially delaying decline in GFR
  - protein restriction with adequate caloric intake in order to limit endogenous protein catabolism

- **medical**
  - adjust dosages of renally excreted medications
  - HTN: ACEI (target 130/80 or less), loop diuretics when GFR <25 mL/min
  - dyslipidemia: statins
  - calcium and phosphate disorders:
    - calcium supplements (e.g. TUMS®) treats hypocalcemia when given between meals and binds phosphate when given with meals
    - consider calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic
    - sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
    - vitamin D analogues are being introduced in the near future
    - cinacalcet for hyperparathyroidism (sensitizes parathyroid to Ca²⁺, decreasing PTH)
  - metabolic acidosis: sodium bicarbonate
  - anemia: erythropoietin injections (Hct <30%); target Hct 33-36%
  - clotting abnormalities: DDAVP if patient has clinical bleeding or invasive procedures (acts to reverse platelet dysfunction)
  - dialysis (hemodialysis, peritoneal dialysis)
  - renal transplantation

### Renin Angiotensin System Blockade and Cardiovascular Outcomes in Patients with Chronic Kidney Disease and Proteinuria: A Meta-Analysis

**Am Heart J** 2008;155:791-805

**Purpose:** To evaluate the role of RAS blockade in improving cardiovascular CV outcomes in patients with CKD.

**Study Selection:** Randomized controlled trials that analyzed CV outcomes in patients with CKD/proteinuria treated with RAS blockade (ACEI/ARB). RAS blockade-based therapy was compared with placebo and control therapy (β-blocker, calcium-channel blockers, and other antihypertensive-based therapy) in the study.

**Results:** Twenty-five trials (n=45,758) were included. Compared to placebo, RAS blockade reduced the risk of heart failure in patients with diabetic nephropathy. In patients with non-diabetic CKD, RAS blockade decreased CV outcome compared to control therapy.

**Conclusions:** RAS blockade reduced CV outcomes in diabetic nephropathy as well as non-diabetic CKD.
Prevention of Progression
- as above
- control of HTN, DM, cardiovascular risk factors (e.g. smoking cessation)
- avoid nephrotoxins
- address reversible causes of AKI

End Stage Renal Disease
- end stage renal disease represents a decline in kidney function which can occur over days to weeks (AKI), over months to years (CKD), or as a combination of the two

Presentation of End Stage Renal Disease

1. Volume Overload
- due to increase in total body Na⁺ content
- signs: weight gain, HTN, pulmonary or peripheral edema

2. Electrolyte Abnormalities
- high
  ▪ K⁺ (decreased renal excretion, increased tissue breakdown)
  ▪ PO₄⁻ (decreased renal excretion, increased tissue breakdown)
  ▪ Ca²⁺ (rare; happens during recovery phase after rhabdomyolysis-induced AKI or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
- low
  ▪ Na⁺ (failure to excrete excessive water intake)
  ▪ Ca²⁺ (decreased Vit D activation, hyperphosphatemia, hypoalbuminemia)
  ▪ HCO₃⁻ (especially with sepsis or severe heart failure)

3. Uremic Syndrome
- manifestations result from retention of urea and other metabolites as well as hormone deficiencies

Figure 19. Signs and symptoms of end stage renal disease
**Complications**

- CNS: decreased LOC, stupor, seizure
- CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- GI: peptic ulcer disease, gastroduodenitis, AVM
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
- endocrine
  - decreased testosterone, estrogen, progesterone
  - increased FSH, LH
- metabolic
  - renal osteodystrophy: secondary increased PTH due to decreased Ca\(^{2+}\), high PO\(_{4}^{3-}\), and low active vitamin D
  - osteitis fibrosa cystica
  - hypertriglyceridemia, accelerated atherogenesis
  - decreased insulin requirements, increased insulin resistance
- dermatologic: pruritus, ecchymosis, hematoma, calciphylaxis (vascular Ca\(^{2+}\) deposition)

---

**Renal Replacement Therapy**

### Indications for Dialysis in Chronic Kidney Disease

**Table 14. Indications for Dialysis**

<table>
<thead>
<tr>
<th>Absolute Indications</th>
<th>Relative Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Volume overload(^*)</td>
<td>• Anorexia</td>
</tr>
<tr>
<td>• Hyperkalemia(^*)</td>
<td>• Decreased cognitive functioning</td>
</tr>
<tr>
<td>• Severe metabolic acidosis(^*)</td>
<td>• Profound fatigue and weakness</td>
</tr>
<tr>
<td>• Neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures)</td>
<td>• Severe anemia unresponsive to erythropoietin</td>
</tr>
<tr>
<td>• Uremic pericarditis</td>
<td>• Persistent severe pruritus</td>
</tr>
<tr>
<td>• Refractory accelerated HTN</td>
<td>• Restless leg syndrome</td>
</tr>
<tr>
<td>• Clinically significant bleeding diathesis</td>
<td></td>
</tr>
<tr>
<td>• Persistent severe N/V</td>
<td></td>
</tr>
<tr>
<td>• Plasma Cr &gt;12 mg/dL (1060 µmol/L) or Urea &gt;100 mg/dL (36 mEq/L; clinical picture also important)</td>
<td></td>
</tr>
</tbody>
</table>

\(^*\)Unresponsive to medications

- **Hemodialysis**: blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  - available as intermittent (e.g. 3x/wk), continuous (CVVHD) or sustained low efficiency (SLED)
  - can be delivered at home or in-center, nocturnal
  - vascular access can be achieved through a central line, an artificial graft, or an AV fistula
  - patients with CKD should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >4.0 mg/dL (>350 µmol/L), or within 1 yr of an anticipated need

- **Peritoneal dialysis**: peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  - advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  - available as continuous ambulatory (CAPD; four exchanges per day) or cyclic (CCPD; machine carries out exchanges overnight)

- refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)

---

**How to Write Dialysis Orders**

(MUST BE INDIVIDUALIZED)

- Filter Type (e.g. FRD)
- Length (e.g. 4 h 3x/wk or 2 h daily)
- Q Blood Flow (max 500 cc/min)
- Ultrafiltration (e.g. 2 L or to target dry weight)
- Na\(^+\) 140 (can be adjusted by starting at 155 and “ramping” down to minimize cramping)
- K\(^+\) (based on serum K\(^+\))
  - Serum K\(^+\) Dialysate
  - 4-6 1.5
  - 3.5-4 2.5
  - <3.5 3.5
- Ca\(^{2+}\) 1.25
- HCO\(_{3}^{-}\) 40
- Heparin (none, tight [500 U/h] or full [1000 U/h])
- IV fluid to support BP (e.g. N/S)
Table 15. Peritoneal Dialysis vs. Hemodialysis

<table>
<thead>
<tr>
<th></th>
<th>Peritoneal Dialysis</th>
<th>Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate</strong></td>
<td>Slow</td>
<td>Fast</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Home</td>
<td>Hospital (usually)</td>
</tr>
<tr>
<td><strong>Ultrafiltration</strong></td>
<td>Osmotic pressure via dextrose dialysate</td>
<td>Hydrostatic pressure</td>
</tr>
<tr>
<td><strong>Solute Removal</strong></td>
<td>Concentration gradient and convection</td>
<td>Concentration gradient and convection</td>
</tr>
<tr>
<td><strong>Membrane</strong></td>
<td>Peritoneum</td>
<td>Semi-permeable artificial membrane</td>
</tr>
<tr>
<td><strong>Method</strong></td>
<td>Intervening catheter in peritoneal cavity</td>
<td>Line from vessel to artificial kidney</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Infection at catheter site</td>
<td>Vascular access (clots, collapse)</td>
</tr>
<tr>
<td></td>
<td>Bacterial peritonitis</td>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Metabolic effects of glucose</td>
<td>Bleeding due to heparin</td>
</tr>
<tr>
<td></td>
<td>Difficult to achieve adequate clearance in patients with large body mass</td>
<td>Hemodynamic stress of extracorporeal circuit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disseminated syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/water flux over short time)</td>
</tr>
<tr>
<td><strong>Preferred When</strong></td>
<td>Young, high functioning, residual renal function</td>
<td>Bed-bound, comorbidities, no renal function</td>
</tr>
<tr>
<td></td>
<td>Success depends on presence of residual renal function</td>
<td>Residual renal function not as important</td>
</tr>
</tbody>
</table>

Renal Transplantation

- Provides maximum replacement of GFR
- Preferred modality of RRT in CKD, not AKI
  - Best way to reverse uremic signs and symptoms
  - Only therapy shown to improve survival in CKD patients with ESRD
- Native kidneys usually left in situ
- 2 types: deceased donor, living donor (related or unrelated)
- Kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- 1 yr renal allograft survival rates ≥90%

Complications

- Leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
- #1 cause of mortality in transplanted patients is cardiovascular disease
- Immunosuppressant drug therapy: side effects include infections, malignancy (skin, Kaposi's sarcoma, post-transplant lymphoproliferative disorder)
- Acute rejection: graft site tenderness, rise in Cr, oliguria, ± fever, although symptoms are uncommon
- De novo GN (usually membranous)
- New-onset DM (often due to prednisone use)
- Cyclosporine or tacrolimus nephropathy (refer to Small Vessel Disease, NP18)
- Chronic allograft nephropathy
  - Early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
  - Immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset DM)
  - Transplant glomerulopathy from antibody injury causes nephrotic proteinuria
- CMV (cytomegalovirus) infection and other opportunistic infections usually occur between 1 and 6 mo post-transplant
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss

Commonly Used Immunosuppressive Drugs

- Calcineurin inhibitors
  - Cyclosporine
  - Tacrolimus
- Antiproliferative medications
  - Mycophenolate mofetil
  - Azathioprine
- Other agents
  - Sirolimus
  - Prednisone
- Anti-lymphocyte antibodies
  - Thymoglobulin
  - Basiliximab

Survival Among Nocturnal Home Hemodialysis Patients Compared to Kidney Transplant Recipients

- *Nephrol Dial Transplant* 2009;24:2915-2919
- Study: Retrospective, matched cohort with 4-5 yr average follow up.
- Population: 177 nocturnal home dialysis (NHD) patients (mean age 46, 68% white) were matched to 533 deceased donor transplant (DTX) patients and 533 live donor (LTX) transplant patients (1:3:3 ratio).
- Intervention: Nocturnal home dialysis vs. live or deceased donor transplant.
- Outcome: Primary outcome was all cause mortality.
- Results: No significant difference in survival or hazard ratio between NHD and DTX. Significant survival benefit for patients undergoing LTX vs. NHD. Significant mortality hazard ratio reduction with LTX (0.51) with no difference in hazard ratio for DTX vs. NHD reference.
- Conclusion: NHD has comparable mortality to DTX, but is inferior to LTX.
### Table 16. Common Medications in Nephrology

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
<th>Site of Action</th>
<th>Mechanism of Action (Secondary Effect)</th>
<th>Indication</th>
<th>Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td>furosemide (Lasix®)</td>
<td>Thick ascending limb of Loop of Henle</td>
<td>± Na⁺/K⁺/2Cl⁻ transport ± renal and peripheral vasodilatory effects (K⁺ loss; ↑ H⁺ secretion; ↑ Ca²⁺ excretion)</td>
<td>Management of edema secondary to CHF, nphoretic syndrome, cindrotic ascites; ↑ free water clearance (e.g. in SIADH-induced hyponatremia), ↑ BP (less effective due to short action)</td>
<td>furosemide: edema: 20-80 mg IV/IM/PO q6-8h (max 600 mg/d) until desired response HTN: 20-80 mg/d PO OD/bid dosing</td>
<td>Allergy in sulfa-sensitive individuals Electrolyte abnormalities; hyponatremia, hypernatremia, hypocalcemia, hypercalciremia (with stone formation) Volume depletion with metabolic alkalosis Precipitates gouty attacks</td>
</tr>
<tr>
<td></td>
<td>bumetanide (Bumex®)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>chlorothiazide (DiuTz®)</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>hydrochlorothiazide (HCTZ)</td>
<td></td>
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<tr>
<td></td>
<td>indapamide (Lozid®, Lozide®)</td>
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<td>metolazone (Zaroxolyn®)</td>
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<td></td>
<td>chlorothalidone (Hygroton®)</td>
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<tr>
<td><strong>Thiazide Diuretics</strong></td>
<td>hydrochlorothiazide (HCTZ)</td>
<td>Distal convoluted tubule</td>
<td>Inhibit Na⁺/Cl⁻ transporter (K⁺ loss; ↑ H⁺ secretion; ↑ Ca²⁺ excretion)</td>
<td>1st line for essential HTN</td>
<td>HCTZ: edema: 25-100 mg PO OD HTN: 12.5-25 mg PO OD (max 50 mg/d)</td>
<td>Hypokalemia Increased serum urate levels Precipitates gouty attacks, hypercalcaemia Elevated lipids Glucose intolerance</td>
</tr>
<tr>
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<td>chlorothiazide (DiuTz®)</td>
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<td></td>
<td>indapamide (Lozid®, Lozide®)</td>
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<td>metolazone (Zaroxolyn®)</td>
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<td></td>
<td>chlorothalidone (Hygroton®)</td>
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<tr>
<td><strong>Potassium-Sparing Diuretics</strong></td>
<td>spironolactone (Aldactone®)</td>
<td>Cortical collecting duct (↓ Na⁺ reabsorption)</td>
<td>Aldosterone antagonist Closes apical Na⁺ channels directly Reduces K⁺ loss caused by other diuretics Edema/hypervolemia Severe CHF, ascites (spironolactone), cystic fibrosis (amiloride + viscosity of secretions)</td>
<td></td>
<td>spironolactone: 25-200 mg/d OD/bid dosing HTN: 50-200 mg/d OD/bid dosing Hyperaldosteronism: 100-400 mg/d OD/bid dosing amiloride: edema/HTN: 5-10 mg PO OD</td>
<td>Hyperkalemia (caution with ACEI) Triamterene can be nephrotoxic (rare) Nephrolithiasis Gynecomastia (estrogenic effect of spironolactone)</td>
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<tr>
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<td>triamterene (Bytename®)</td>
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<td>amiloride (Midamor®)</td>
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<tr>
<td><strong>Combination Agents</strong></td>
<td>Dyazide® (triamterene + HCTZ)</td>
<td></td>
<td></td>
<td>Combine ACEI with thiazide for synergistic effect</td>
<td>Combine K⁺-sparring drug with thiazide to reduce hypokalemia</td>
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<td></td>
<td>Aldactazide® (spironolactone + HCTZ)</td>
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<td>Moduretic® (amiloride + HCTZ)</td>
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<td>Vasotec® (enalapril + HCTZ)</td>
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<td>Zestoretic® (lisinopril + HCTZ)</td>
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<tr>
<td><strong>Osmotic Diuretics</strong></td>
<td>mannitol (Gentrol®)</td>
<td>Renal tubules (proximal and collecting duct)</td>
<td>Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate – inhibits reabsorption of water and ↑ urinary excretion of toxic materials</td>
<td>To ↓ intracranial or intraocular pressure Mobilization of excess fluid in renal failure or edematous states</td>
<td>mannitol: i/iv: 0.25-2 g/kg IV over 30-60 min</td>
<td>Transient volume expansion Electrolyte abnormalities (↓ Na⁺, ↓ K⁺)</td>
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<tr>
<td></td>
<td>glycerol urea</td>
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<tr>
<td><strong>ACEI</strong></td>
<td>ramipril (Altace®)</td>
<td>Lungs Tissues diffusely</td>
<td>Prevents angiotensin II vasoconstricting vascular smooth muscle → net vasoconstriction → ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na⁺ and H₂O excretion → ↓ BP Reduces fibrosis and atherogenesis</td>
<td>HTN Cardioprotective effects (see Cardiology and Cardiac Surgery) Renoprotective effects</td>
<td>ramipril: HTN: 2.5-20 mg PO OD/bid dosing renoprotective use: 10 mg PO OD</td>
<td>Cough Asthma Hyperkalemia Angioedema Agranulocytosis (captopril) Akinol Teratogenic</td>
</tr>
<tr>
<td></td>
<td>enalapril (Vasotec®)</td>
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<td>lisinopril (Prinivil®)</td>
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<td>trandolapril (Mavik®)</td>
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<td></td>
<td>captopril (Capoten®)</td>
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<tr>
<td><strong>ARB</strong></td>
<td>losartan (Cozar®)</td>
<td>Vascular smooth muscle, adrenal cortex, proximal tubules</td>
<td>Competitive inhibitor at the angiotensin II receptor: prevents angiotensin II vasoconstricting action on vascular smooth muscle → ↓ BP Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na⁺ and H₂O excretion</td>
<td>HTN Cardioprotective effects (see Cardiology and Cardiac Surgery) Renoprotective effects</td>
<td>HTN: losartan 25-100 mg PO OD candesartan 8-32 mg PO OD ibersartan 150-300 mg PO OD valsartan 80-320 mg PO OD telmisartan 20-80 mg PO OD eprosartan 400-800 mg PO OD olmesartan 20-40 mg PO OD</td>
<td>Hyperkalemia Cough – reduce dose in hepatic impairment Akinol Teratogenic</td>
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<tr>
<td></td>
<td>candesartan (Atacand®)</td>
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<td>ibersartan (Avapro®)</td>
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<td>valsartan (Diovan®)</td>
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<td>telmisartan (Micardis®)</td>
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<td>eprosartan (Teveten®)</td>
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<tr>
<td></td>
<td>olmesartan (Dioctic®)</td>
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<tr>
<td><strong>Renin Antagonists</strong></td>
<td>aliskiren (Rasilez®)</td>
<td>Direct renin antagonist</td>
<td>Prevents renin production and activity Cardioprotective and renoprotective abilities being evaluated</td>
<td>HTN Cardioprotective effects (see Cardiology and Cardiac Surgery) Renoprotective effects</td>
<td>aliskiren 150-300 mg PO OD</td>
<td>Hyperkalemia</td>
</tr>
</tbody>
</table>
### Landmark Nephrology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D</td>
<td>NEJM 2005; 353:238-48</td>
<td>Patients with type 2 DM receiving maintenance hemodialysis were randomized to 20 mg of atorvastatin per day or matching placebo; no difference in composite index of death from cardiac causes, nonfatal myocardial infarction, and stroke</td>
</tr>
<tr>
<td>AASK</td>
<td>JAMA 2001; 285:2719-28</td>
<td>Ramipril, compared with amlopidine, slows progression of hypertensive renal disease and proteinuria and may benefit patients without proteinuria as well</td>
</tr>
<tr>
<td>ACCOMPUSH</td>
<td>NEJM 2008; 359:2417-20</td>
<td>Combination treatment with an ACEI and a CCB (benazapril-amlodipine) was more successful than a combination of ACEI and a thiazide diuretic (benzapril-HCTZ) in reducing cardiovascular events in patients with HTN who were at risk for such events</td>
</tr>
<tr>
<td>ACEI and Diabetic</td>
<td>NEJM 1993; 329:1456-62</td>
<td>Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood pressure control alone</td>
</tr>
<tr>
<td>ALERT</td>
<td>Lancet 2003; 361:2024-31</td>
<td>The use of fluvastatin in renal transplant recipients did not significantly decrease the risk of the occurrence of a major adverse cardiac event (defined as cardiac death, non-fatal MI, or coronary intervention procedure) compared with placebo; however, there was a significant reduction in cardiac deaths or non-fatal MI</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>Early Termination (Unpublished Results; protocol – NTD 2009; 24:1663-71)</td>
<td>Combining Aliskiren with ACEI or ARB in high-risk patients with type 2 DM leads to increased incidence of nonfatal stroke, hypokalemia, and hypotension</td>
</tr>
<tr>
<td>ASTRAL</td>
<td>NEJM 2009; 361:1953-62</td>
<td>Renal artery revascularization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality, and carries significant operative risks</td>
</tr>
<tr>
<td>AURORA</td>
<td>NEJM 2009; 360:1395-407</td>
<td>Patients receiving maintenance hemodialysis randomized to rosuvastatin 10 mg daily or placebo; rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
</tr>
<tr>
<td>BENEDICT</td>
<td>NEJM 2004; 351:1941-51</td>
<td>Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 DM and HTN with normoalbuminuria</td>
</tr>
<tr>
<td>CHORI</td>
<td>NEJM 2006; 355:2085-98</td>
<td>Patients with CKD were randomly assigned to receive a dose of epopet alfa targeted to achieve a hemoglobin level of 13.5 g/dl or 11.3 g/dl; the higher target group had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), or stroke</td>
</tr>
<tr>
<td>CREATE</td>
<td>NEJM 2006; 355:2071-84</td>
<td>Patients with CKD (15-35 mL/min) and mild to moderate anemia (11-12.5 g/dL) were randomized to normal (13-15 g/dL) or sub-normal (10.5-11.5 g/dL) hemoglobin levels; early and complete correction of hemoglobin did not reduce the risk of cardiovascular events</td>
</tr>
<tr>
<td>DETAIL</td>
<td>NEJM 2004; 351:1952-61</td>
<td>The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 DM with mild to moderate HTN and early nephropathy</td>
</tr>
<tr>
<td>ELITE-SYMPOHNY</td>
<td>NEJM 2007; 357:2562-75</td>
<td>Darcluzumab induction, MMF, steroids, and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNI regimens</td>
</tr>
<tr>
<td>FHN</td>
<td>NEJM 2010:363:2287-300</td>
<td>Patients were randomized to dialysis 6x/wk (frequent) or 3x/wk (conventional); frequent hemodialysis was associated with improvement in composite outcomes of death, or change in left ventricular mass and death, or change in a physical-health composite score; frequent hemodialysis caused more frequent interventions related to vascular access</td>
</tr>
<tr>
<td>HEMO</td>
<td>NEJM 2002; 347:2010-19</td>
<td>Use of high dose dialysis or high flux membranes vs. standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes; possible benefit in cardiac-related outcomes with high flux membranes</td>
</tr>
<tr>
<td>IDEAL</td>
<td>NEJM 2010; 363:609-19</td>
<td>Patients with progressive CKD and GFR between 10 and 15 mL/min randomized to initiate dialysis at GFR of 10-14 mL/min (early) or 5-7 mL/min (late); early initiation of dialysis in patients with stage G5 CKD was not associated with an improvement in survival or clinical outcomes</td>
</tr>
<tr>
<td>IDNT</td>
<td>NEJM 2001; 345:851-60</td>
<td>Treatment with irbesartan reduced the risk of developing end-stage renal disease and worsening renal function in patients with type 2 DM and diabetic nephropathy</td>
</tr>
<tr>
<td>IRMA</td>
<td>NEJM 2001; 345:870-8</td>
<td>Irbesartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 DM and microalbuminuria</td>
</tr>
<tr>
<td>MDRD</td>
<td>Ann Intern Med 1995; 122:754-62</td>
<td>Patients with proteinuria of more than 1 g/d should have a target BP &lt;125/75 mmHg; patients with proteinuria of 0.25-1.0 g/d should have a target BP &lt;130/80 mmHg</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Lancet 2008; 372:547-53</td>
<td>Telmisartan and ramipril monotherapy reduced proteinuria and rise in Cr in patients with high vascular risk; combination of the two agents led to increased acute renal failure episodes, syncope, and hypotension</td>
</tr>
<tr>
<td>REIN</td>
<td>Lancet 1999; 354:359-64</td>
<td>In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria</td>
</tr>
<tr>
<td>REIN2</td>
<td>Lancet 2005; 365:939-46</td>
<td>In non-diabetic nephropathy already on ACEI, no further benefit from intensified BP control (sBP/dBP&lt;130/80 mmHg) by adding a CCB vs. conventional BP control (sBP&lt;90 mmHg) on ACEI alone</td>
</tr>
<tr>
<td>RENAAAL</td>
<td>NEJM 2001; 345:861-9</td>
<td>Losartan conferred significant renal benefits in patients with type 2 DM and nephropathy and was generally well-tolerated</td>
</tr>
<tr>
<td>RENAL</td>
<td>NEJM 2009; 361:1627-38</td>
<td>High intensity continuous renal-replacement therapy in AKI does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia</td>
</tr>
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</table>
Roadmap Nephrology Landmark Nephrology Trials/References Essential Med Notes 2015

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROAD</td>
<td>JASN 2007; 18:1889-98</td>
<td>Uptitration of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without DM who had proteinuria and renal insufficiency.</td>
</tr>
<tr>
<td>ROADMAP</td>
<td>NEJM 2011; 364:907-17</td>
<td>The use of the ARB olmesartan was more effective than placebo in delaying the onset of microalbuminuria in patients with type 2 DM, normoalbuminuria, and good blood pressure control; however, a higher rate of fatal cardiovascular events was found amongst patients with preexisting coronary heart disease in the olmesartan group.</td>
</tr>
<tr>
<td>SHARP</td>
<td>Lancet 2011; 377:2181-92</td>
<td>Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization took simvastatin 20 mg plus ezetimibe 10 mg daily vs. matching placebo; simvastatin 20 mg plus ezetimibe 10 mg daily resulted in reduction of LDL cholesterol with associated reduction of major atherosclerotic events in patients with CKD.</td>
</tr>
<tr>
<td>TREAT</td>
<td>NEJM 2009; 361:2019-32</td>
<td>Patients with type 2 DM, CKD, and anemia were randomized to darbepoetin targeting a hemoglobin of 13 g/dL or placebo; darbepoetin did not reduce the risk of death, a cardiovascular event, or a renal event, and was associated with an increased risk of stroke.</td>
</tr>
</tbody>
</table>

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Donadio JV, Grande DP. Medical progress: IgA nephropathy. NEJM 2002;347:739-748.
ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. NEJM 2008;359:1547-1559.
Scherer M. Seminars for year 3 University of Toronto Medicine clinical clerk on medicine: hypertension and hypernatremia. October 29, 2002.

ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. NEJM 2008;359:1547-1559.
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The Neurological Exam

**General Exam and Mental Status**

- **vitals**: pulse (especially rhythm), BP, temperature
- **H&N**: meningismus, head injury/bruises (signs of basal skull fracture: Battle's sign, raccoon eyes, hemotympanum, CSF rhinorrhea/otorrhea), tongue biting
- **CVS**: carotid bruits, heart murmurs
- **mental status**: orientation (person, place, time), LOC (GCS)
  - GCS/15 – Motor/6, Verbal/5 (T= intubated), Eyes/4
- **cognition**
  - Folstein MMSE – /30 (note: dementia is a clinical diagnosis and is not diagnosed by cognitive testing)
  - MoCA – /30 (≥26 is considered normal)
  - frontal lobe testing (for perseveration)
  - clock drawing

**Cranial Nerves Exam**

- **olfactory** (CN I): odor sensation (test each nostril separately)
- **optic** (CN II)
  - a. visual acuity: test each eye individually using best corrected vision
  - b. visual fields
  - c. pupil: direct and consensual pupillary reaction (afferent limb), accommodation, swinging flashlight test (see Relative Afferent Pupillary Defect, *Ophthalmology*, OP33)
  - d. fundoscopy: optic disc edema, optic disc pallor, exudates, hemorrhages
- **extraocular movements** (EOM)
  - a. oculomotor (CN III): levator palpebrae superioris, medial rectus, superior rectus, inferior rectus, inferior oblique, efferent limb of pupillary light response
  - b. trochlear (CN IV): superior oblique
  - c. abducens (CN VI): lateral rectus
- **trigeminal** (CN V)
  - a. sensory: V1 (above supraorbital ridge), V2 (buccal area), V3 (mandible), corneal reflex (afferent)
  - b. motor: temporalis, masseter, pterygoids, jaw jerk reflex
- **facial** (CN VII)
  - a. sensorimotor: muscles of facial expression, hyperacusis (stapedius), corneal reflex (efferent)
  - b. visceral sensory: taste of anterior 2/3 of tongue
  - c. visceral motor: salivary and lacrimal glands
- **vestibulocochlear** (CN VIII)
  - a. vestibular: nystagmus, caloric reflexes
  - b. cochlear: Rinne, Weber
- **glossopharyngeal** (CN IX) and **vagus** (CN X): palatal elevation, gag reflex, vocal cord function, swallowing, taste at posterior third of tongue
- **accessory** (CN XI): trapezius and sternocleidomastoid strength
- **hypoglossal** (CN XII): tongue muscle bulk, fasciculations, strength

**Motor Exam**

- **bulk**: atrophy, asymmetry
- **abnormal movements**: asymmetry of movement (suggests weakness, e.g. satellite sign), tremors, chorea, dystonia, hemiballism, myoclonus, ataxia, tics, fasciculations
- **abnormal posturing**: decerebrate, decorticate
- **tone**: hypotonia (flaccid), hypertonia (spasticity, rigidity, paratonia), cogwheeling (rigidity + tremor)
- **strength**
- **reflexes**: deep tendon reflexes, abdominal reflexes, primitive reflexes, Babinski, Hoffman, clonus
Table 1. Localization of Motor Deficits

<table>
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<tr>
<th></th>
<th>LMN</th>
<th>UMN</th>
<th>Extrapyramidal</th>
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<tr>
<td>Muscle Tone</td>
<td>Flaccid</td>
<td>Spastic</td>
<td>Rigid</td>
</tr>
<tr>
<td>Involuntary Movements</td>
<td>Fasciculations</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Decreased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Plantar Reflex</td>
<td>Down-going (flexor)</td>
<td>Up-going (extensor)</td>
<td>Down-going (flexor)</td>
</tr>
<tr>
<td>Pattern of Muscle Weakness</td>
<td>Proximal, distal, or focal</td>
<td>Upper extremities: extensors weaker than flexors</td>
<td>Lower extremities: flexors weaker than extensors</td>
</tr>
</tbody>
</table>

Table 2. Overview of Neuromuscular Diseases

<table>
<thead>
<tr>
<th>Upper and Lower Motor Neuron Disease</th>
<th>Peripheral Neuropathy</th>
<th>Neuromuscular Junction</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Segmental and asymmetrical, distal → proximal</td>
<td>Distal (except GBS) but may be asymmetrical</td>
<td>Proximal and fatiguable, or weak then recovers (e.g. LEMS)</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Increased</td>
<td>Decreased/absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Sensory</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Autonomic*</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 3. Approach to Strength Testing of Radiculopathies vs. Peripheral Neuropathies

How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, all associated peripheral nerves (and their movements) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerve. Particularly useful peripheral nerve “pairs” are bolded for emphasis.

<table>
<thead>
<tr>
<th>Root</th>
<th>Peripheral Nerve</th>
<th>Movement</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Axillary</td>
<td>Shoulder abduction</td>
<td>Deltoide</td>
</tr>
<tr>
<td>C6</td>
<td>Musculocutaneous (C5/6) Radial (C6)</td>
<td>Elbow flexion</td>
<td>Biceps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elbow flexion</td>
<td>Brachioradialis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wrist extension</td>
<td>Extensor carpi radialis longus</td>
</tr>
<tr>
<td>C7</td>
<td>Radial</td>
<td>Elbow extension</td>
<td>Triceps</td>
</tr>
<tr>
<td></td>
<td>Posterior interosseus</td>
<td>Finger extension</td>
<td>Extensor digitorum communis</td>
</tr>
<tr>
<td>C8, T1</td>
<td>Median</td>
<td>Thumb flexion</td>
<td>Flexor pollicis longus (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td>Ulnar</td>
<td>Thumb abduction</td>
<td>Abductor pollicis brevis (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opposition</td>
<td>Opponens pollicis (look for thenar wasting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finger abduction</td>
<td>First dorsal interosseus (look for wasting in first dorsal webbed space)</td>
</tr>
<tr>
<td>L2, 3, 4</td>
<td>Femoral Obturator</td>
<td>Hip flexion</td>
<td>Iliopsoas</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hip adduction</td>
<td>Adductor muscles</td>
</tr>
<tr>
<td>L3, 4</td>
<td>Femoral (L3/4) Deep peroneal (L4/5)</td>
<td>Knee extension</td>
<td>Quadriceps</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dorsiflexion</td>
<td>Tibialis anterior</td>
</tr>
<tr>
<td>L5</td>
<td>Sciatic (L5, S1)</td>
<td>Hip extension</td>
<td>Gluteus maximus</td>
</tr>
<tr>
<td></td>
<td>Osgood</td>
<td>Ankle inversion</td>
<td>Tibialis posterior</td>
</tr>
<tr>
<td></td>
<td>Superficial</td>
<td>Ankle inversion</td>
<td>Peroneal muscles</td>
</tr>
<tr>
<td></td>
<td>peroneal</td>
<td>Deep peroneal</td>
<td>Big toe extension</td>
</tr>
<tr>
<td>S1</td>
<td>Sciatic</td>
<td>Knee flexion</td>
<td>Hamstring muscles</td>
</tr>
<tr>
<td></td>
<td>Tibial</td>
<td>Plantar flexion</td>
<td>Gastrocnemius and soleus</td>
</tr>
</tbody>
</table>

Sensory Exam

- primary sensation
  - spinothalamic tract: pain and temperature
  - dorsal column: proprioception and vibration
- cortical sensation
  - graphesthesia, stereognosis, extinction, 2-point discrimination
Coordination Exam and Gait

- coordination exam
  - finger-to-nose, heel-to-shin, rapid alternating movements
- stance and gait
  - gait: antalgic, hemiplegic, ataxic, apraxic, festination, foot drop, broad-based
  - tandem gait (heel-to-toe walking)
  - Romberg test
  - pull test for postural instability

Basic Anatomy Review

- Romberg Test
  Stable with eyes open and closed = normal
  Stable with eyes open, falls with eyes closed = positive Romberg, suggesting loss of joint position sense

- Common Cerebellar Findings
  Frontal executive dysfunction/ disinhibition, scanning speech, nystagmus, hypo- or hypermetric saccades, hypotonia, pendular reflexes, terminal tremor, ataxic finger-nose/heel-shin/tandem, wide based stance, positive rebound

- Interpreting a Slow or Uncoordinated Rapid Alternating Movement (RAM)
  - Slow RAMs without fatiguing is suggestive of weakness (especially if it is asymmetric)
  - Slow RAMs with fatiguing (i.e. decreasing amplitude over time) is suggestive of Parkinsonism
  - Uncoordinated RAM is suggestive of cerebellar disorder (i.e. ataxia and irregularly irregular rhythm) or ideomotor apraxia
Internal capsule
Upper motor neurons
in motor cortex
Pyramids
Medial corticospinal tract
Lateral corticospinal tract
Decussation of the pyramids (medulla)
Lower motor neuron
Limb muscles
Axial muscles

Internal capsule
Pyramids
Medial corticospinal tract
Lateral corticospinal tract
Decussation of the pyramids (medulla)
Lower motor neuron
Limb muscles
Axial muscles

Within 1-2 spinal levels of their entry, axons of first order neurons synapse onto second order neurons, whose axons then decussate before ascending as the spinothalamic tract.

Figure 3. Discriminative touch pathway (dorsal column) from body
Figure 4. Spinothalamic tract from body
Figure 5. Discriminative touch pathway (dorsal column) from face
Figure 6. Spinothalamic tract pathway from face
Figure 7. Corticospinal motor pathway
Figure 8. Sympathetic and parasympathetic pathway

Sympathetic
- Dilation
- Constriction
- Lachrymal and salivary glands
- Pupil
- Dilation
- Constriction
- Lacrimal and salivary glands
- Pterygopalatine g. (lacrimation)
- Submaxillary g. (salivation)
- Otic g. (parotid secretion)
- Bronchodilation
- Secretion
- Coronary arteries and heart rate
- Vasodilation
- Acceleration
- Vasoconstriction
- Deceleration
- Glycogen utilization
- Bile secretion
- GI tract
- Inhibit motility and enzyme secretion
- Stimulate motility and enzyme secretion
- Adrenal medulla
- Bladder
- Inhibit
- Constriction
- Constriction
- Piloerector
- Vasoconstriction
- Sweat glands
- stimulated
- Liver
- Skin
- Release
- epinephrine

Parasympathetic
- Modulate secretion
- Lacrimal and salivary glands
- Pterygopalatine g. (lacrimation)
- Submaxillary g. (salivation)
- Otic g. (parotid secretion)
- Lungs and trachea
- Pterygopalatine g. (lacrimation)
- Modulate secretion
- Otic g. (parotid secretion)
- Bronchodilation
- Secretion
- Coronary arteries and heart rate
- Vasodilation
- Acceleration
- Vasoconstriction
- Deceleration
- Glycogen utilization
- Bile secretion
- GI tract
- Inhibit motility and enzyme secretion
- Stimulate motility and enzyme secretion
- Adrenal medulla
- Bladder
- Inhibit
- Constriction
- Constriction
- Piloerector
- Vasoconstriction
- Sweat glands
- stimulated
- Liver
- Skin
- Release
- epinephrine

Figure 9. Dermatome map

Myotomes
- C5 – Shoulder abduction/ elbow flexion
- C6 – Wrist extensors
- C7 – Elbow extension
- C8 – Squeeze hand
- T1 – Finger abduction
- T2-9 – Intercostal (abdominal reflexes)
- T9-10 – Upper abdominals
- T11-12 – Lower abdominals
- L2 – Hip flexion
- L3 – Hip adduction
- L4 – Knee extension and ankle dorsiflexion
- L5 – Ankle dorsiflexion and big toe extension
- S1 – Plantarflexion
Lumbar Puncture

Indications
- diagnostic: CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barré, vasculitis), subarachnoid hemorrhage (if CT negative), CNS neoplasm (neoplastic meningitis)
- therapeutic: to administer anesthesia, chemotherapy, contrast media; to decrease ICP (pseudotumor cerebri, normal pressure hydrocephalus)

Contraindications
- mass lesion causing ICP - could lead to cerebral herniation
  - require CT first
- infection over LP site/suspected epidural abscess
- low platelets (<50,000) or treatment with anticoagulation (high INR or aPTT)
- uncooperative patient

Complications
- tonsillar herniation (rare)
- subdural hematoma
- post-LP headache (5-40%): worse when upright, better supine; generally onset within 24 h
  - prevention: smaller gauge (i.e. 22) needle, reinsert stylet prior to needle removal, blunt-ended needle
  - symptomatic treatment: caffeine and sodium benzoate injection
  - corrective treatment: blood patch (autologous)
- spinal epidural hematoma
- infection

LP Tubes
- tube #1: cell count and differential: RBCs, WBCs, and differential
  - xanthochromia (yellow bilirubin pigmentation implies recent bleed into CSF)
- tube #2: chemistry: glucose (compare to serum glucose) and protein
- tube #3: microbiology: Gram stain and C&S
  - specific tests depending on clinical situation/suspicion
    - viral: PCR for herpes simplex virus (HSV) and other viruses
    - bacterial: polysaccharide antigens of H. influenzae, N. meningitidis, S. pneumoniae
    - fungal: Cryptococcal antigen, culture
    - TB: acid-fast stain, TB culture, TB PCR
- tube #4: cytology: for evidence of malignant cells
- tube #5: cell count: compare RBC count to that of tube #1
  - note: tube 4 or 5 can be sent for repeat cell count

Table 4. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Color</th>
<th>Protein</th>
<th>Glucose</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>Clear</td>
<td>&lt;0.45 g/L</td>
<td>60% of serum glc or</td>
<td>0-5 x 10^6/L WBC, 0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;54 mg/dL</td>
<td>RBC, 0 PMNs</td>
</tr>
<tr>
<td>INFECTIOUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Infection</td>
<td>Clear or opalescent</td>
<td>Normal or slightly increased</td>
<td>&lt;0.45-1 g/L</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
<td>&lt;1,000 x 10^6/L</td>
</tr>
<tr>
<td>Bacterial Infection</td>
<td>Opalescent yellow, may clot</td>
<td>&gt;1 g/L</td>
<td>Decreased (&lt;25% serum glc or &lt;36 mg/dL)</td>
<td>&gt;1,000 x 10^6/L PMNs</td>
</tr>
<tr>
<td>Granulomatous Infection (tuberculosis, fungal)</td>
<td>Clear or opalescent</td>
<td>Increased but usually &lt; 5 g/L</td>
<td>Decreased (usually &lt;36-72mg/dL)</td>
<td>&lt;1,000 x 10^6/L Lymphocytes</td>
</tr>
</tbody>
</table>

Approach to Common Presentations

Weakness

Approach
- mode of onset: abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (hereditary, degenerative, endocrinologic, neoplastic)
- course: worse at onset (vascular), progressive (neoplastic, degenerative, infective), episodic (vascular, inflammatory), activity dependent (NMJ, muscular)
- pattern: objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
- associated symptoms: sensory symptoms, cortical symptoms, spinal symptoms (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
- history: family history, developmental history, medications, risk factors, recent/preceding exposures
- investigations for LMN: NCS/EMG
- investigations for UMN: imaging (brain and/or spinal cord)
Differential Diagnosis
• objective muscle weakness; also, differentiate between true muscle weakness vs. fatigue
  ▪ generalized
    • myopathy (proximal > distal weakness)
      – endocrine: hypothyroidism, hyperthyroidism, Cushing’s syndrome
      – rheumatologic: polymyositis, vasculitis
      – infectious: HIV, CMV, influenza
    – other: collagen vascular disorders, steroids, statins, alcohol, electrolyte disorders
  ▪ NMJ (MG, botulism, LEMS, organophosphate poisoning)
  ▪ cachexia
  ▪ localized
    • UMN (leukodystrophy, vasculitis, abscess, brain tumor, vitamin B12 deficiency, MS, stroke)
    • radicular pain (i.e. nerve root)
    • anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic, lead toxicity)
    • peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
• no objective muscle weakness
  ▪ chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  ▪ depression, deconditioning
• if loss of passive motion, consider intra-articular, peri-articular, or extra-articular causes

Numbness/Altered Sensation
Approach
• positive sensory symptoms: paresthesia/dysesthesia = tingling, pins and needles, pricking, burning, stabbing
  • negative sensory symptoms: hypoesthesia/anesthesia = numbness, diminution, or absence of feeling
• determine distribution of sensory loss
  ▪ nerve root vs. peripheral nerve?
  ▪ symmetric stocking-glove pattern? (indicative of distal symmetric polyneuropathy)
  ▪ anterior-posterior spinal cord dissociation
• investigations: NCS, vitamin B12 levels, imaging based on associated findings

Differential Diagnosis
• cerebral: stroke, demyelination, tumor
  ▪ associated symptoms: hemiplegia, aphasia, apraxia
• brainstem: stroke, demyelination, tumor
  ▪ associated symptoms: diplopia, vertigo, dysarthria, dysphagia
• spinal cord/radiculopathy: cord infarction, tumor, MS, syringomyelia, vitamin B12 deficiency, disc lesion
  ▪ associated symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern)
• neuropathy: focal compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, vitamin B12 deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid

Cranial Nerve Deficits

CN I: Olfactory Nerve

Clinical Features
• absence of sense of smell associated with a loss of taste

Differential Diagnosis
• nasal: physical obstruction
  ▪ heavy smoking, chronic rhinitis, sinusitis, neoplasms, septal deformity, choanal atresia, vestibular stenosis, foreign body
• olfactory neuroepithelial: destruction of receptors or their axon filaments
  ▪ influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
• central: lesion of olfactory pathway
  ▪ Kallmann’s syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeval inflammation, meningioma, aneurysm, PA stroke, MS
• endocrine/metabolic
  ▪ DM, adrenal hypo/hyperfunction, pseudohypoparathyroidism, hypothyroidism, renal/liver failure, vitamin deficiency
CN II: Optic Nerve

- see Neuro-Ophthalmology, N12

CN III: Oculomotor Nerve

Clinical Features
- ptosis, resting eye position is “down and out” (depressed and abducted), pupil dilated (mydriasis)
- vertical and horizontal diplopia; paralysis of adduction, elevation, and depression

Differential Diagnosis
- PComm aneurysm: early mydriasis, then CN III palsy
- cavernous sinus (internal carotid aneurysm, meningioma, sinus thrombosis): associated with deficits in other CNs near the cavernous sinus
- ischemia of CN III (DM, temporal arteritis, HTN, atherosclerosis): pupil sparing CN III palsy
- midbrain lesion: complete unilateral CN III palsy with bilateral weakness of the superior rectus and ptosis with contralateral pyramidal signs ± mydriasis
- orbital lesion: associated with optic neuropathy, chemosis, proptosis
- other (inflammatory, infection, neoplasia, uncal herniation, trauma)

Figure 11. Cavernous sinus (coronal view)

CN IV: Trochlear Nerve

Clinical Features
- vertical and torsional diplopia; defect of intorsion and depression
- patient may complain of difficulty going down stairs or reading

Differential Diagnosis
- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, superior orbital fissure (tumor, granuloma)

CN V: Trigeminal Nerve

Clinical Features
- ipsilateral facial numbness, weakness of muscles of mastication (V3 only) with pterygoid deviation towards the side of the lesion

Differential Diagnosis
- brainstem (ischemia, tumor, syringobulbia, demyelination)
- peripheral (tumor, aneurysm, chronic meningitis, metastatic infiltration of nerve)
- trigeminal ganglion (acoustic neuroma, meningioma, fracture of middle fossa)
- cavernous sinus (carotid aneurysm, meningioma, sinus thrombosis)
- trauma
- note: other CN V lesions that cause facial pain = trigeminal neuralgia, herpes zoster

CN VI: Abducens Nerve

Clinical Features
- resting inward deviation (esotropia)
- horizontal diplopia; defect of lateral gaze

Pupillary constrictor fibers run along outside of nerve, whereas vasculature is contained within nerve
For CN III palsy with a reactive pupil, always think ischemic cause (“pupil sparing”)
For CN III palsy with mydriasis, think compressive lesion

DDx of CN III Palsy
iCAM ischemic Cavernous sinus Aneurysm (PComm, internal carotid) Midbrain lesion

Lesions involving the cavernous sinus can lead to cranial nerve palsies of III, IV, V1, and V2 as well as orbital pain, and proptosis

CN IV is the only cranial nerve that crosses the midline and exits posteriorly
A CN IV lesion may cause a contralateral deficit

CN IV is at risk of trauma during neurosurgical procedures involving the midbrain because of its long intracranial course

Jaw deviation is towards the side of a LMN CN V lesion

Distinguishing CN III, IV, and VI Lesions

<table>
<thead>
<tr>
<th></th>
<th>III</th>
<th>IV</th>
<th>VI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diplopia</td>
<td>Oblique</td>
<td>Vertical</td>
<td>Horizontal</td>
</tr>
<tr>
<td>Excoriating</td>
<td>Near target down</td>
<td>Looking down</td>
<td>Far target</td>
</tr>
<tr>
<td>Head Tilt</td>
<td>Up and rotated away</td>
<td>Down and flexed away</td>
<td>Rotated towards</td>
</tr>
</tbody>
</table>

CN VI has the longest intracranial course and is vulnerable to increased ICP, creating a false localizing sign
Differential Diagnosis

- **pons** (infarction, hemorrhage, demyelination, tumor): associated with facial weakness and contralateral pyramidal signs
- **tentorial orifice** (compression, meningioma, trauma): false localizing sign of increased ICP
- **cavernous sinus** (carotid aneurysm, meningioma, sinus thrombosis)
- **ischemia of CN VI** (DM, temporal arteritis, HTN, atherosclerosis)
- **congenital** (Duane’s syndrome)

**CN VII: Facial Nerve**

Clinical Features

- LMN lesion: ipsilateral facial weakness (facial droop, flattening of forehead, inability to close eyes, flattening of nasolabial fold)
- UMN lesion: contralateral facial weakness with forehead sparing (due to bilateral frontalis innervation)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

Differential Diagnosis

- **idiopathic** = Bell’s palsy, 80-90% of cases (see Otolaryngology, OT23)
  - most often related to HSV, but other viruses may be implicated (CMV, herpes zoster, EBV)
- **other**: temporal bone fracture, EBV, Ramsay Hunt (HSV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease, Lyme meningitis, HIV

**CN VIII: Vestibulocochlear Nerve**

- see Otolaryngology, OT14

**CN IX: Glossopharyngeal Nerve**

Clinical Features

- unilateral lesion is rare
- taste dysfunction in posterior 1/3 of tongue
- absent gag reflex and dysphagia

Disorders

- **glossopharyngeal neuralgia**: sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
  - treated with carbamazepine or surgical ablation of CN IX

Uvula deviation is away from the side of a LMN CN X lesion due to impaired ipsilateral palatal elevation
**CN X: Vagus Nerve**

**Clinical Features**
- oropharyngeal dysphagia (transfer dysphagia) due to palatal and pharyngeal weakness
  - neuromuscular causes of dysphagia
    - CNS: stroke, cerebral palsy, tumor, trauma, PD, AD, MS
    - CN: DM, laryngeal nerve palsy, polio, ALS
    - myopathic/NMJ: dermatomyositis, polymyositis, MG, sarcoidosis
  - other causes of dysphagia: see Gastroenterology, G8
- dysarthria: inability to produce understandable speech due to impaired phonation and/or resonance

**CN XI: Accessory Nerve**

**Clinical Features**
- LMN lesion: paralysis of ipsilateral trapezius and sternocleidomastoid (ipsilateral shoulder drop, weakness on turning head to contralateral side)
- UMN lesion: paralysis of ipsilateral sternocleidomastoid and contralateral trapezius

**CN XII: Hypoglossal Nerve**

**Clinical Features**
- LMN lesion: tongue deviation towards lesion; ipsilateral tongue atrophy and fasciculations (if chronic)
- UMN lesion: tongue deviation away from lesion; absence of atrophy and fasciculations

### Table 5. Cranial Nerve Examination and Associated Deficits

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Recommended Physical Exams</th>
<th>Signs/Symptoms of Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory (CN I)</td>
<td>Odor sensation: test each nostril separately</td>
<td>Anosmia (should be associated with loss of taste)</td>
</tr>
<tr>
<td>Optic (CN II)</td>
<td>Visual acuity: test each eye individually; best corrected vision Test visual fields Assess pupils: direct and consensual pupillary reaction (afferent), RAPD (swinging flashlight test) Fundoscopy: optic disc edema and pallor, venous pulsations, hemorrhages</td>
<td>Blindness Absence of light reflexes</td>
</tr>
<tr>
<td>Oculomotor (CN III)</td>
<td>Assess extraocular movements and nystagmus Test efferent limb of pupillary light response Assess size and shape of pupils; accommodation and saccadic eye movements</td>
<td>Eyes deviated down and out; can demonstrate mydriasis</td>
</tr>
<tr>
<td>Trochlear (CN IV)</td>
<td>Test movement of superior oblique</td>
<td>Vertical diplopia; may tilt head towards unaffected side; affected eye cannot turn inward and downward</td>
</tr>
<tr>
<td>Trigeminal (CN V)</td>
<td>Test sensation above supraorbital ridge (V1), buccal area (V2), mandible (V3) Test corneal reflex (afferent limb) Assess motor function: temporalis, masseter, pterygoids, jaw jerk reflex</td>
<td>Loss of facial sensations and corneal reflex on stimulation ipsilaterally Weakness and wasting of muscles of mastication; deviation of open jaw to ipsilateral side; trigeminal neuralgia</td>
</tr>
<tr>
<td>Abducens (CN VI)</td>
<td>Test movement of lateral rectus</td>
<td>Horizontal diplopia, esotropia (convergent strabismus), and abductor paralysis of ipsilateral eye</td>
</tr>
<tr>
<td>Facial (CN VII)</td>
<td>Sensorimotor nerve function: to muscles of facial expression Test efferent limb of corneal reflex Visceral sensory nerve function: to anterior 2/3 of the tongue Visceral motor nerve function: to salivary and lacrimal glands</td>
<td>Paralysis of ipsilateral upper and lower facial muscles Loss of lacrimation Decreased salivation, dry mouth Loss of taste to anterior 2/3 of the tongue ipsilaterally LMN lesion = ipsilateral facial weakness UMN lesion = contralateral facial weakness, sparing the brow bilaterally</td>
</tr>
<tr>
<td>Vestibulocochlear (CN VIII)</td>
<td>Vestibular function (nystagmus, caloric) Cochlear function (Rinne, Weber)</td>
<td>Vertigo, disequilibrium, and nystagmus Neural deafness</td>
</tr>
<tr>
<td>Glosso-Pharyngeal (CN IX)</td>
<td>Assess vocal cord function and gag reflex Assess taste to posterior third of the tongue (bitter and sour taste)</td>
<td>Loss of taste in posterior third of the tongue ipsilaterally Loss of gag reflex and dysphasia Unilateral lesion is rare</td>
</tr>
<tr>
<td>Vagus (CN X)</td>
<td>Assess vocal cord function and gag reflex Observe usula deviation and palatal elevation Assess swallowing</td>
<td>Loss of gag reflex, dysphagia, hoarse voice Paralysis of soft palate (failed elevation) Deviation of usula to contralateral side of lesion; anesthesia of pharynx and larynx ipsilaterally</td>
</tr>
<tr>
<td>Accessory (CN XI)</td>
<td>Assess strength of trapezius (shoulder shrug) and sternocleidomastoid muscles (head turn)</td>
<td>Ipsilateral shoulder weakness and turning head to opposite side</td>
</tr>
<tr>
<td>Hypoglossal (CN XII)</td>
<td>Inspect tongue for signs of lateral deviation, atrophy, fasciculations, asymmetry of movement and strength</td>
<td>Wasting of ipsilateral tongue muscles and deviation to ipsilateral side on protrusion</td>
</tr>
</tbody>
</table>
NEURO-OPHTHALMOLOGY

Abnormalities of Vision

- see Ophthalmology, OP3

Acute Visual Loss

- see Ophthalmology, OP3

Optic Neuritis

- see Optic Disc Edema below, Multiple Sclerosis, N52

Anterior Ischemic Optic Neuropathy

- see Optic Disc Edema
- non-arteritic (NAION): due to atherosclerosis
- arteritic (AION): due to giant cell arteritis (see Rheumatology, RH20)

Amaurosis Fugax

- see Ophthalmology, OP37 and Stroke, N47

Central Retinal Vein Occlusion

- see Ophthalmology, OP24

Optic Disc Edema

Table 6. Common Causes of Optic Disc Edema

<table>
<thead>
<tr>
<th>Optic Neuritis</th>
<th>Papilledema</th>
<th>AION</th>
<th>CRVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;50 yr</td>
<td>Any</td>
<td>&gt;50 yr but usually &gt;70 yr</td>
</tr>
<tr>
<td>Vision</td>
<td>Rapidly progressive monocular central vision loss with ↓ acuity and color vision with recovery</td>
<td>Late visual loss</td>
<td>Painless unilateral acute field defect over hours to days with ↓ color vision</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Pain (especially with eye movement)</td>
<td>H/A, N/V, local neurological deficits</td>
<td>If GCA: H/A, scalp tenderness, jaw claudication, weight loss, fatigue</td>
</tr>
<tr>
<td>Pupil</td>
<td>RAPD</td>
<td>No RAPD</td>
<td>RAPD</td>
</tr>
<tr>
<td>Fundus</td>
<td>Disc swelling if anterior Normal disc if retrobulbar</td>
<td>Bilateral disc swelling, retinal hemorrhage, no venous pulsations</td>
<td>Pale segmental disc edema, retinal dot, flame hemorrhages</td>
</tr>
<tr>
<td>Etiologies</td>
<td>MS, viral</td>
<td>Increased ICP</td>
<td>Giant cell arteritis Non-arteritic: atherosclerosis</td>
</tr>
<tr>
<td>Investigations</td>
<td>MRI with gadolinium</td>
<td>Emergent CT, LP if CT is normal to measure opening pressure</td>
<td>CBC, ESR, CRP, temporal artery biopsy</td>
</tr>
<tr>
<td>Treatment</td>
<td>IV methylprednisolone</td>
<td>Treat cause</td>
<td>Consider ASA if non-arteritic; steroids if arteritic</td>
</tr>
</tbody>
</table>

If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results. Begin treatment immediately.

NAION can be caused by use of Sildenafil (Viagra®) in rare cases.
Optic Disc Atrophy

- **etiologies**: glaucoma, AION, compressive tumor, optic neuritis, Leber’s hereditary optic neuropathy, congenital
- **presentation**: disc pallor, low visual acuity, peripheral vision defect, decreased color vision
- **treatment**: none (irreversible), aim to prevent

Abnormalities of Visual Field

![Visual Fields Defects](image)

- **Right anopsia** (right optic nerve lesion)
- **Right anopsia and left upper quadrantanopsia** (junctional scotoma)
- **Bitemporal hemianopsia** (chiasmal lesion)
- **Left homonymous hemianopsia** (right optic tract lesion)
- **Left upper quadrantanopsia** (right temporal lesion)
- **Left lower quadrantanopsia** (right parietal lesion)

Abnormalities of Eye Movements

Disorders of Gaze

**Pathophysiology**
- horizontal gaze: FEF → contralateral PPRF (midbrain/pons) → eyes saccade away from FEF
- vertical gaze: cortex → rostral interstitial nucleus in the MLF (midbrain)

**Clinical Features**
- unilateral lesion in one FEF → eyes deviate toward the side of the lesion
  - can be overcome with doll’s eye maneuver
- unilateral lesion in the PPRF → eyes deviate away from the lesion
  - cannot be overcome with doll’s eye maneuver if CN VI nucleus lesion as well
- seizure involving a FEF: eyes deviate away from the focus

**Etiology**
- common: infarcts (frontal or brainstem), MS, tumors

Internuclear Ophthalmoplegia

**Pathophysiology**
- results from a lesion in MLF which disrupts coordination between CN VI nucleus in pons and the contralateral CN III nucleus in midbrain → disrupts conjugate horizontal gaze

**Clinical Features**
- horizontal diplopia on lateral gaze, oscillopsia
- on gaze away from the side of the lesion
  - ipsilateral adduction defect
  - contralateral abduction nystagmus
- cannot be overcome by caloric testing
- accommodation reflex intact
- may be bilateral (especially in MS)

**Etiology**
- common: MS, brain stem infarct

**Investigations**
- MRI

Bitemporal Hemianopsia DDx by Age
- **Children**: craniopharyngioma
- **Middle aged (20s to 50s)**: pituitary mass
- **Elderly (>60 yr)**: meningioma

In homonymous hemianopsia, more congruent deficits are caused by more posterior lesions. Mucular sparing may occur with occipital lesions

Check all hemiplegic patients for homonymous hemianopsia (ipsilateral to side of hemiplegia)

A lesion in a cerebral hemisphere causes eyes to “look away” from the hemiplegia, and to look towards the lesion

A lesion in the brainstem causes the eyes to “look toward” the side of the hemiplegia, and to look away from the lesion

Internuclear Ophthalmoplegia

- to medial rectus m.
- to lateral rectus m.
- Vergence (normal)
  - Right gaze (normal)
  - Left gaze (abnormal → right SDV)

Figure 13. Characteristic visual field defects with lesions along the visual pathway

Figure 14. Internuclear ophthalmoplegia
Diplopia

Etiology – Monocular
• mostly due to relatively benign optical problems (refractive error, cataract) or functional

Etiology – Binocular (due to ocular misalignment)
• muscle
  □ Graves’ ophthalmopathy
  □ EOM restriction/entrapment
• neuromuscular junction
  □ MG (see Myasthenia Gravis, N37)
• cranial nerve palsy (see Cranial Nerve Deficits, N8)
• INO (see Intranuclear Ophthalmoplegia, N13)
• other
  □ orbital trauma (orbital floor fracture), tumor, infection, inflammation
  □ Miller-Fisher variant of GBS
  □ Wernicke’s encephalopathy
  □ leptomeningeal disease

Approach to Diplopia
• monocular vs. binocular
• horizontal vs. vertical vs. oblique diplopia
• direction of gaze that exacerbates diplopia
• corrective head movements

Workup
• may observe isolated 4th or 6th nerve palsy for a few weeks, but workup if persistent or other symptoms develop
• indications for neuroimaging
  □ bilateral or multiple nerve involvement
  □ severe sudden onset headache (rule out aneurysm)

Nystagmus

• definition: rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
• direction of nystagmus is labeled by the rapid component of the eye movement
• can be categorized by movement type (pendular, jerking, rotatory, coarse) or as physiological vs. pathological

<table>
<thead>
<tr>
<th>Table 7. Nystagmus Features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Direction</td>
</tr>
<tr>
<td>Vertical Nystagmus</td>
</tr>
<tr>
<td>Gaze Fixation</td>
</tr>
<tr>
<td>Vertigo</td>
</tr>
<tr>
<td>Auditory Symptoms</td>
</tr>
<tr>
<td>Other Neurological Signs</td>
</tr>
<tr>
<td>DDx</td>
</tr>
</tbody>
</table>

Abnormalities of Pupils

• see Ophthalmology, OP30
Nutritional Deficiencies and Toxic Injuries

• sufficient nutritional intake is required for optimal nervous system functioning; deficiencies in
  the following key nutrients, among others, may impair central and peripheral nervous system
  function (potential neurological symptoms are provided)

Table 8. Nutritional Deficiency Features and Management

<table>
<thead>
<tr>
<th>Vitamin Deficiency</th>
<th>Neurological Clinical Manifestation</th>
<th>Investigation</th>
<th>Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12</td>
<td>Paresthesias and a sensory ataxia are the most common initial symptoms</td>
<td>Serum cobalamin; Serum methylmalonic acid; Serum homocysteine</td>
<td>IM Vitamin B12 1,000 μg for 5 d, then once per mo or oral B12 1,000 μg/d</td>
</tr>
<tr>
<td>Folate</td>
<td>Myeloneuropathy, peripheral neuropathy</td>
<td>Serum folate; Homocysteine</td>
<td>Oral folate 1 mg tid initially; 1 mg daily thereafter</td>
</tr>
<tr>
<td>Copper</td>
<td>Myelopathy, pyramidal signs (e.g. brisk muscle stretch reflexes at the knees and extensor plantar responses) Severe sensory loss</td>
<td>Serum copper and seruloplasmin; urinary copper</td>
<td>Discontinue zinc; oral copper 8 mg/d for 1 wk; 6 mg/d for 1 wk; 4 mg/d for 1 wk; 2 mg/d thereafter</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Ophthalmoplegia, retinopathy, spino-cerebellar syndrome with peripheral neuropathy (with signs of cerebellar ataxia)</td>
<td>Serum vitamin E; ratio serum vitamin E to sum of cholesterol and triglycerides</td>
<td>Vitamin E 2,200 mg/kg/d oral or IM</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Three well-described manifestations include: beriberi (dry and wet), infantile beriberi, Wernicke encephalopathy with Korsakoff syndrome Alcoholism is a cause of reduced intake of thiamine, leading to deficiency</td>
<td>Clinical diagnosis; brain MRI</td>
<td>Thiamine 100 mg IV followed by 50-100 mg IV or IM until nutritional status stable</td>
</tr>
<tr>
<td>Pyridoxine (Vitamin B6)</td>
<td>Painful sensorimotor peripheral neuropathy</td>
<td>Serum pyridoxal phosphate</td>
<td>Pyridoxine 50-100 mg daily</td>
</tr>
<tr>
<td>Niacin</td>
<td>Encephalopathy, coma, and peripheral neuropathy</td>
<td>Urinary excretion niacin metabolites</td>
<td>Nicotinic acid 25-50 mg daily oral or IM</td>
</tr>
</tbody>
</table>

*IM = intramuscular; IV = intravenous

• it is also important to consider occupational neurotoxic syndromes secondary to exposure to
  pesticides, solvents, and metals. Encephalopathy, extrapyramidal features, neurodegenerative
  diseases, and peripheral neuropathy are commonly encountered. Onset and progression
  of neurological diseases should be temporally related to neurotoxin exposure. Main toxins
  associated with neurotoxicity are listed below:

Table 9. Selected Occupational Neurotoxic Syndromes

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Associated Occupations</th>
<th>Characteristic Neurological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organic solvents</td>
<td>Printer, spray painters, industrial cleaners, paint or glue manufacturers, graphic industry, electronic industry, plastic industry</td>
<td>Nausea, H/A, concentration difficulty Long-term exposure may lead to “chronic solvent-induced encephalopathy”, characterized by mild-to-severe cognitive impairment</td>
</tr>
<tr>
<td>Pesticides (e.g. insecticides, fungicides, rodenticides, fumigants, herbicides)</td>
<td>Agricultural work, pesticide manufacturing and formulating employees, highway and railway workers, green house, forestry and nursery workers</td>
<td>Parkinson’s disease risk increased by ~70% following pesticide exposure</td>
</tr>
<tr>
<td>Metals (e.g. lead, mercury, manganese, aluminum, arsenic)</td>
<td>Battery and metal production (e.g. solder, pipes), chemical and electronic application industries, steel manufacturing, welders, alloy workers, transportation, packaging, construction</td>
<td>Lead: delayed or reversed development, permanent learning disabilities, seizures, coma, death from encephalopathy (rare) Mercury: psychiatric disturbances, ataxia, visual loss, hearing loss, tiredness, memory disturbances Manganese: psychiatric symptoms, hallucinations (“manganese madness”), extrapyramidal features, dystonia, parkinsonism (manganese) Aluminum: implicated in Alzheimer’s pathogenesis Arsenic: sleeplessness/sleepiness, irritability, H/A, spasms in muscle extremities and muscle fatigue</td>
</tr>
<tr>
<td>Gases (e.g. carbon dioxide, nitrous oxide, formaldehyde)</td>
<td>Anesthesia, disinfection, manufacture of illuminating gas and water gas</td>
<td>Cognitive/behavioral and emotional symptoms, parkinsonian syndromes</td>
</tr>
</tbody>
</table>

Neurologic Complications due to Toxic Injuries Related to Bariatric Surgery

• deficiencies of both fat- and water-soluble vitamins may occur following malabsorptive bariatric surgery
• patients who have undergone malabsorptive surgery should be monitored for late metabolic complications and neurological manifestations
Seizure Disorders and Epilepsy

**Seizure**

**Definitions**
- **seizure**: transient neurological dysfunction caused by excessive activity of cortical neurons, resulting in paroxysmal alteration of behavior and/or EEG changes
- **epilepsy**: chronic condition characterized by two or more unprovoked seizures

**Classification**

![Classification of seizures](image)

NOTE: seizures can also be classified using age of onset (childhood/adolescence, adulthood/late [i.e. >-age 30]), setting (sleep, upon awakening), EEG (focal, generalized)

**Signs and Symptoms**
- **partial seizures**
  - simple or complex can secondarily generalize, or simple → complex → generalized seizures
  - **simple (preserved LOC)**
    - motor: postural, phonatory, forceful turning of eyes and/or head, focal muscle rigidity/jerking  ± Jacksonian march (spreading to adjacent muscle groups)
    - sensory: unusual sensations affecting vision, hearing, smell, taste, or touch
    - autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
    - psychiatric: symptoms rarely occur without impairment of consciousness and are more commonly complex partial
  - **complex (altered LOC)**
    - patient may appear to be awake but with impairment of awareness
    - classic complex seizure is characterized by automatisms such as chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing, and other stereotypic movements
    - other forms: dysphasic, dysmnesic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness
- **generalized seizures (decreased LOC)**
  - **absence (petit mal)**: usually only seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - **clonic**: repetitive rhythmic jerking movements
  - **tonic**: muscle rigidity in flexion or extension
  - **tonic-clonic** (grand mal, generalized tonic-clonic [GTC])
    - prodrome of unease or irritability hours to days before the episode
    - tonic ictal phase: muscle rigidity
    - clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence
    - post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours
  - **myoclonic**: sporadic contractions localized to muscle groups of one or more extremities
  - **atonic**: loss of muscle tone leading to drop attack

**Medical Emergency**
Status epilepticus can cause irreversible brain damage without treatment

**Stroke**
Stroke is the most common cause of late-onset (>50 yr) seizures, accounting for 50-80% of cases

**Seizures and Dementia**
Neurodegenerative diseases can underlie seizures; conversely, seizures can be a cause of dementia

**Complex partial status epilepticus**
Can resemble schizophrenia or psychotic depression

**Temporal lobe epilepsy**
Suggested by an aura of fear, olfactory or gustatory hallucinations, and visceral or déjà vu sensations

**Frontoparietal cortex seizures**
Suggested by contralateral focal sensory or motor phenomena

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Suggested by contralateral focal sensory or motor phenomena
Table 10. Classic Factors Differentiating Seizure vs. Syncope

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Onset</td>
<td>Day or night</td>
<td>Day</td>
</tr>
<tr>
<td>Position</td>
<td>Any</td>
<td>Upright, not recumbent</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden or brief</td>
<td>Gradual</td>
</tr>
<tr>
<td>Aura</td>
<td>Possible specific aura</td>
<td>Lightheaded sensation</td>
</tr>
<tr>
<td>Color</td>
<td>Normal or cyanotic</td>
<td>Pallor</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Uncommon outside of ictal phase</td>
<td>Common; diaphoresis</td>
</tr>
<tr>
<td>Duration</td>
<td>Brief or prolonged</td>
<td>Brief</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Common</td>
<td>Possible but rare</td>
</tr>
<tr>
<td>Post-ictal</td>
<td>Occurs in tonic-clonic or complex partial</td>
<td>No</td>
</tr>
<tr>
<td>Motor Activity</td>
<td>Common</td>
<td>Occasional brief jerks</td>
</tr>
<tr>
<td>Injury</td>
<td>Common, tongue biting</td>
<td>Rare unless from fall</td>
</tr>
<tr>
<td>Automatisms</td>
<td>Common in absence or complex partial</td>
<td>None</td>
</tr>
<tr>
<td>EEG</td>
<td>Usually abnormal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Table 11. Classic Factors Differentiating Seizure vs. Pseudoseizure (Conversion Disorder)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Pseudoseizure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triggers</td>
<td>Uncommon</td>
<td>Emotional disturbance</td>
</tr>
<tr>
<td>Duration</td>
<td>Brief or prolonged</td>
<td>May be prolonged</td>
</tr>
<tr>
<td>Motor Activity</td>
<td>Synchronous, stereotypic, automatisms, lateral tongue biting, eyes rolled back</td>
<td>Opsiphotonos, rigidity, forced eye closure, irregular extremity movements, shaking head, pelvic thrust, crying, geotrophic eye movements, tongue biting at the tip</td>
</tr>
<tr>
<td>Timing</td>
<td>Day or night</td>
<td>Day; other people present</td>
</tr>
<tr>
<td>Physical Injury</td>
<td>May occur</td>
<td>Rare</td>
</tr>
<tr>
<td>Incontinence</td>
<td>May occur</td>
<td>Rare</td>
</tr>
<tr>
<td>Reproduction of Attack</td>
<td>Spontaneous</td>
<td>Suggestion ± stimulus</td>
</tr>
<tr>
<td>EEG</td>
<td>Often inter-ictal discharges</td>
<td>Normal</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Pseudoseizures do not rule out seizures (not uncommon to present with both)

Investigations
- CBC, electrolytes, fasting blood glucose, Ca²⁺, Mg²⁺, ESR, Cr, liver enzymes, CK, prolactin
- also consider toxicity screen, EtOH level, AED level (if applicable)
- CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
- LP (if fever or meningismus)
- EEG

Treatment
- avoid precipitating factors
- indications for medical therapy (anticonvulsants): 2 or more unprovoked seizures, known organic brain disease, EEG with epileptiform activity, first episode of status epilepticus, abnormal neurologic examination or findings on neuroimaging
- psychosocial issues: stigma of seizures, education of patient and family, status of driver’s license, pregnancy issues
- safety issues: driving, operating heavy machinery, bathing, swimming alone
- consider surgical treatment if focal and refractory

Status Epileptics

- definition: unremitting seizure of greater than 5 min; or successive seizures without return to a baseline state
- complications: anoxia, cerebral ischemia and cerebral edema, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)
- initial measures: ABCs, vitals, monitors, fingerprick glucose (STAT), ECG, nasal O₂, IV NS, IV glucose, IV thiamine, ABGs (if respiratory distress/cyanotic)

20-59% of first EEG are positive in epilepsy; 59-92% of epilepsy is picked up with repeated EEGs; normal interictal EEGs do not rule out epilepsy

Pregnancy Issues
Teratogenicity of anticonvulsants includes neural tube defects, cleft palate, urogenital malformations, and heart defects. Advise patient planning pregnancy to take 5 mg/d of folic acid. Optimize AEDs with lowest possible dose associated with good seizure control, preferably monotherapy if possible. Risk of fetal malformations with AEDs is 2x general population; highest risk associated with valproic acid and/or 2+ concurrent AEDs. Consider pre-conception AED levels if patient is well-controlled, monthly serum levels during pregnancy, and titrate AED to maintain pre-conception serum levels. Refer to high risk OB for intrapartum fetal screening

EEG findings suggestive of epilepsy: abnormal spikes, polyspike discharges, spike-wave complexes

By law, the Ministry of Transportation must be contacted for all patients who have had a seizure; patients will have their license suspended until seizure free for 6 mo; commercial drivers face a longer wait

Note that frontal seizures (rare) can look like a pseudoseizure due to odd motor activity that may occur
• **blood work:** electrolytes, Ca$^{2+}$, Mg$^{2+}$, PO$_4^{3-}$, glucose, CBC, toxicology screen, EtOH level, AED levels
• **focused history:** onset, past history of seizures, drug and alcohol ingestion, past medical history, associated symptoms, witnesses/collateral history
• **physical exam** (once seizures controlled): LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (rule out injuries)

### Disorders of Consciousness

#### Definition
- the minimally conscious state and the vegetative state are disorders of consciousness that can be acute and reversible or chronic and irreversible (Bernat, 2006)
- the vegetative state is defined as a state of wakefulness without awareness, while the minimally conscious state is described as wakefulness with transient low levels of awareness to stimuli
- the three main clinical features of vegetative state are:
  A. cycle of eye opening and closing (indicative of a sleep-wake cycle)
  B. complete lack of awareness of self or the environment (i.e. no evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli)
  C. complete or partial preservation of hypothalamic and brain stem autonomic functions
- those in a vegetative state also show no evidence of language comprehension or expression, and have bowel and bladder incontinence, but have variably preserved cranial-nerve and spinal reflexes
- a vegetative state is considered persistent if it lasts longer than 1 mo and permanent when it lasts longer than six mo for non-traumatic brain injuries and 1 yr for traumatic brain injuries

#### Etiology
- may develop suddenly (consequence of traumatic or non-traumatic injury), or gradually (in the course of a neurodegenerative disorder)
- may involve diffuse lesions to cortical neurons, thalami, or white matter tracts

#### Epidemiology
- vegetative state: 0.2-3.4 per 100,000
- minimally conscious state: 1.4 per 100,000

---

**Figure 17. Status epilepticus treatment algorithm**

**Antiepileptic Drugs**
- **generalized-onset and partial-onset seizures:** felbamate, lamotrigine, levetiracetam, refinamide, topiramate, valproate, zonisamide
- **partial seizures** (simple partial, complex partial, and secondarily generalized seizures): carbamazepine, gabapentin, lacosamide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, vigabatrin (note: these drugs may exacerbate generalized seizures)
- **absence seizures:** ethosuximide

---

**The locked-in syndrome is not a disorder of consciousness but rather a mimic; these individuals have normal sleep-wake cycles, normal levels of awareness, and may exhibit meaningful behavior (via vertical eye-movements and blinking), but are isolated due to quadriplegia and pseudobulbar palsy**
Table 12. Selected Intracranial Causes of Acute Confusion

<table>
<thead>
<tr>
<th>No Awareness</th>
<th>Minimal Awareness</th>
<th>Normal Awareness</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Arousal</td>
<td>Coma, sleep, anesthesia</td>
<td></td>
</tr>
<tr>
<td>Normal Arousal</td>
<td>Vegetative state</td>
<td>Minimally conscious state</td>
</tr>
</tbody>
</table>

### Behavioral Neurology

- see Psychiatry, PS16

### Acute Confusional State/Delirium

Table 13. Selected Intracranial Causes of Acute Confusion

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Subarachnoid hemorrhage</td>
<td>Thunderclap H/A, increased ICP, meningeal signs</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>Focal neurological signs</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td>Infectious</td>
<td>Meningitis</td>
<td>Fever, H/A, nausea, photophobia, meningeal signs</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Focal neurological signs</td>
<td>Fever, H/A, ± seizure</td>
</tr>
<tr>
<td>Abscess</td>
<td>Increased ICP, meningeal signs</td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>Diffuse axonal shear, epidural hematoma, subdural hematoma</td>
<td>Trauma Hx, increased ICP, meningeal signs</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Acute CNS vasculitis</td>
<td>Skin rash, active joints</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Onset: Psychiatric features, memory loss, seizures</td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Mass effect/edema, hemorrhage, seizure</td>
<td>Increased ICP, meningeal signs, papilledema</td>
</tr>
<tr>
<td>Seizure</td>
<td>Status epilepticus</td>
<td>See Seizure Disorders and Epilepsy, N16</td>
</tr>
<tr>
<td>Primary Psychiatric</td>
<td>Psychotic disorder, mood disorder, anxiety disorder</td>
<td>No organic signs or symptoms</td>
</tr>
<tr>
<td>Other</td>
<td>Drugs (e.g. cocaine)</td>
<td>Chest pain, cough with black sputum, new-onset seizure, HTN, increased ICP, dyspnea</td>
</tr>
<tr>
<td></td>
<td>Medications (with anticholinergic side effects)</td>
<td>Flushing, dry skin and mucous membranes, mydriasis with loss of accommodation</td>
</tr>
</tbody>
</table>

Delirium is a medical emergency carrying significant risk of morbidity and mortality; it is characterized by acute onset, disorientation, fluctuating level of consciousness, poor attention, and marked psychomotor changes.

Visual hallucinations more commonly indicate organic disease.

Major Neurocognitive Disorder (formerly Dementia)

- see Psychiatry, PS17

**Definition**

- an acquired, generalized, and (usually) progressive impairment of cognitive function (i.e. memory, recall, orientation, language, abstraction) associated with impairment in activities of daily living (i.e. planning, shopping, food preparation, difficulties with finances)
- affects comprehension, but not level of consciousness

**Causes of Neurocognitive Disorder**

- NCD due to Alzheimer’s disease
- NCD with Lewy bodies
- Vascular NCD
- Other causes of NCD (traumatic brain injury, substance/medication use, HIV infection, prion disease, Parkinson’s disease, Huntington’s disease)

**Major Neurocognitive Disorder**

- Frontotemporal Neurocognitive Disorder
- Executive function
- Behavior: Apathy, disinhibition
- Language: Memory, semantic dementia, non-fluent progressive aphasia

Figure 18. Dementia classification
Diagnosis of Major NCD requires presence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
A) concern of the individual or a knowledgeable informant AND
B) a substantial impairment in cognitive performance either documented by standardized neuropsychological testing or quantified clinical assessment
• see Psychiatry, PS17 for DSM-5 diagnostic criteria
• see Geriatric Medicine, GM3
differentiated from mild NCD (formerly mild cognitive impairment) by the extent to which the impairment affects ADLs
- Mild NCD represents an intermediate stage between dementia and normal aging
- By definition, IADLs are not affected in Mild NCD

Epidemiology
- major NCD (dementia): 1-2% at age 65 and reaching as high as 30% by age 85
- mild NCD: 2-10% at age 65 and 5-25% by age 85
- note
  - Major NCD due to Alzheimer’s disease is uncommon before age 60
  - Major NCD due to frontotemporal lobar degeneration has an earlier onset and represents a progressively smaller fraction of all NCDs with age

Etiology
- see Table 14 for common causes of dementia
- see Table 15 for acquired causes of dementia
- reversible causes: alcohol (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metal toxicity, hepatic or renal failure, B₁₂ deficiency, glucose, cortisol, thyroid dysfunction, normal pressure hydrocephalus, depression (pseudodementia), intracranial tumor, subdural hematoma, hypercalcemia (secondary to elevated PTH)
- must rule out delirium

History
- “geriatric giants”
  - confusion/incontinence/falls/polypharmacy
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects)
  - behavioral (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS
- alcohol, smoking
- OTCs, herbal remedies, medications (sedative hypnotics, antipsychotics, antidepressants, anticholinergics), compliance, accessibility
- history of vascular disease or head trauma
- collateral history

Physical Exam
- blood pressure
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings, cerebrovascular disease
- general physical exam depending on risk factors and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

Investigations
- depends on suspected etiologies (see Tables 13 and 14)
  - CBC (note MCV for evidence of alcohol use and B₁₂ deficiency), glucose, TSH, B₁₂, RBC folate
electrolytes, LFTs, renal function, lipids, serum calcium
  - CT head, MRI as indicated (MRI preferred), SPECT (optional)
  - as clinically indicated: VDRL, HIV, ANA, anti-dsDNA, ANCA, ceruloplasmin, copper, cortisol, toxicology, heavy metals
- issues to consider
  - failure to cope, fitness to drive, caregiver education and stress, power of attorney, legal will, advanced medical directives, patient and caregiver safety

<table>
<thead>
<tr>
<th>Sensitivity and Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tool</td>
</tr>
<tr>
<td>MMSE</td>
</tr>
<tr>
<td>Clinical Judgment</td>
</tr>
<tr>
<td>DSM IV</td>
</tr>
</tbody>
</table>

Vitamin B₁₂ Deficiency Symptoms
- Macrocytic anemia, pallor, SOB, fatigue, chest pain, palpitations
- Confusion or change in mental status (if advanced)
- Decreased vibration sense
- Distal numbness and paresthesia
- Weakness with UMN findings
- Diarrhea, anorexia

Dementia DDx
VITAMIN D VEST
Vitamin deficiency (B₁₂, folate, thiamine)
Intracranial tumor
Trauma (head injury)
Anoxia
Metabolic (DM)
Infection (postencephalitis, HIV)
Normal pressure hydrocephalus
Degenerative (Alzheimer’s, Huntington’s, CJD)
Vascular (multi-infarct dementia)
Endocrine (hypothyroid)
Space occupying lesion (chronic subdural hematoma)
Toxic (alcohol)
Table 14. Common Causes of Major NCD (Dementia)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY DEGENERATIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Memory impairment</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Aphasia, apraxia, agnosia</td>
<td></td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Visual hallucinations</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluctuating cognition</td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia (e.g. Pick’s disease)</td>
<td>Behavioral presentation: Inhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Language presentation: Progressive non-fluent aphasia, semantic dementia</td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Chorea</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>VASCULAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular cognitive impairment (previously Multi-infarct dementia)</td>
<td>Bradyphrenia without features of parkinsonism (slow thinking, slow rate of learning, slow gait)</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Dysexecutive syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be abrupt onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stepwise deterioration is classic but progressive deterioration is most common</td>
<td></td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>Systemic S/S of vasculitis</td>
<td>ANA, ANCA; RF</td>
</tr>
<tr>
<td></td>
<td>CT or MRI</td>
<td>Angiography</td>
</tr>
</tbody>
</table>

Table 15. Acquired Causes of Major NCD (Dementia)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIONAL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic meningitis</td>
<td>Fever, headache, nausea</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Meningism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Localizing neuro deficits</td>
<td></td>
</tr>
<tr>
<td>Chronic encephalitis</td>
<td>Fever, H/A</td>
<td>CT or MRI</td>
</tr>
<tr>
<td>Chronic abscess</td>
<td>Increased ICP</td>
<td>CT with contrast</td>
</tr>
<tr>
<td>HIV</td>
<td>See Infectious Diseases, ID29</td>
<td>HIV serology</td>
</tr>
<tr>
<td>Creutzfeld-Jacob disease</td>
<td>Rapidly progressive, myoclonus</td>
<td>EEG, CT or MRI, LP</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Ataxia, myoclonus, tabes dorsalis</td>
<td>LP, CT, or MRI, VQRI</td>
</tr>
<tr>
<td>TRAUMATIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse axonal shear, epidural hematoma</td>
<td>Trauma Hx, Increased ICP, papiledema</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Localizing neuro signs</td>
<td></td>
</tr>
<tr>
<td>RHEUMATOLOGIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>See Rheumatology, RH11</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ANA, anti-dsDNA</td>
</tr>
<tr>
<td>NEOPLASTIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass effect/edema, hemorrhage, seizure</td>
<td>Increased ICP</td>
<td>CT with contrast</td>
</tr>
<tr>
<td></td>
<td>Localizing neuro signs</td>
<td>MRI</td>
</tr>
<tr>
<td>Paraneoplastic encephalitis</td>
<td>Systemic symptoms of cancer</td>
<td>Anti-Hu antibodies</td>
</tr>
</tbody>
</table>

**Major or Mild NCD due to Alzheimer’s Disease**

- see Psychiatry, PS17

**Definition**

- beyond criterion for NCD, the core features of major or mild NCD due to Alzheimer’s disease include an insidious onset and gradual progression of cognitive and behavioral symptoms
- typical presentation: amnestic (i.e. impairment in memory and learning - impaired ability to learn new information)
  - mild phase: impairment in memory and learning sometimes accompanied with deficits in executive function
  - moderate-severe phase: visuoconstructional/perceptual-motor ability and language may also be impaired
  - social cognition tends to be preserved until late in the course of the disease
• atypical nonamnestic presentation (one of the following)
  a. aphasia: language disturbance
  b. apraxia: impaired ability to carry out motor activities despite intact motor function
  c. agnosia: failure to recognize or identify objects despite intact sensory function
• note: there may be no evidence of mixed etiology (i.e. absence of other neurodegenerative or cerebrovascular disease)

Pathophysiology
• genetic factors
  ▪ minority (<7%) of AD cases are familial (autosomal dominant)
  ▪ 3 major genes for autosomal dominant AD have been identified
    • amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
  ▪ the E4 polymorphism of apolipoprotein E (APOE) is a susceptibility genotype (E2 is protective)
  ▪ note: APOE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
• pathology (although not necessarily specific for AD)
  ▪ diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  ▪ microscopic pathology
    • senile plaques (extracellular deposits of amyloid in the gray matter of the brain)
    • loss of synapses
    • neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated Tau protein)
    • loss of cholinergic neurons in nucleus basalis of Meynert that project diffusely throughout the cortex
  ▪ biochemical pathology
    • 50-90% reduction in action of choline acetyltransferase

Epidemiology
• 1/12 of population 65-75 yr of age
• up to 1/3 population >85 yr of age
• accounts for 60-90% of all dementias (depending on setting and diagnostic criteria)

Risk Factors
• age is the largest risk factor
• genetic susceptibility polymorphism: apolipoprotein E4 increases risk and decreases age of onset
• other factors include: traumatic brain injury, family history, Down syndrome, low education, and presence of multiple vascular risk factors (e.g. smoking, HTN, hypercholesterolemia, DM)

Signs and Symptoms
• cognitive impairment
  ▪ memory impairment for newly acquired information (early)
  ▪ deficits in language, abstract reasoning, and executive function
  ▪ behavioral and psychiatric manifestations (80% of those with major NCD)
    • mild NCD: major depressive disorder and/or apathy
    • major NCD: psychosis, irritability, agitation, combativefulness, and wandering
  ▪ motor manifestations (late)
    • gait disturbance, dysphagia, incontinence, myoclonus, and seizures
    • parkinsonism (if present consider DLB)

Investigations
• perform investigations to rule out other potentially reversible causes of dementia
• EEG: usually normal, may observe generalized slowing (nonspecific)
• MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
• SPECT: hypoperfusion in temporal and parietal lobes
• PET Imaging: imaging using Pittsburgh compound B (PIB) as a tracer enables imaging of beta-amyloid plaque in neuronal tissue

Treatment
• acetylcholinesterase inhibitors have been shown to slow decline in cognitive function
  ▪ donepezil, rivastigmine, galantamine
  ▪ relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers, or risk factors for ulcers, and GI bleeding
  ▪ galantamine is contraindicated in patients with hepatic/renal impairment
• memantine is an NMDA-receptor antagonist that has some benefits in later stage AD (i.e. when MMSE <17)
• symptomatic management
  1. pharmacologic
    ▪ low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
    ▪ trazodone for sleep disturbance
    ▪ antidepressants (SSRIs)
2. non-pharmacologic
   ▪ redirection
   ▪ explore inciting factors for behavior and modify behavior of patient or caregiver
   ▪ family support and day care facilities

Prognosis
- mean duration of survival after diagnosis is approximately 10 yr, reflecting the advanced age of the majority of individuals rather than the course of the disease
- in those who survive the full course, death commonly results from aspiration

Major or Mild NCD with Lewy Bodies
(formerly Dementia with Lewy Bodies)

Definition
- A NCD that includes not only progressive cognitive impairment (with early changes in complex attention and executive function rather than learning and memory), but also recurrent complex visual hallucinations.
- core diagnostic features
  ▪ fluctuating cognition with pronounced variations in attention and alertness
  ▪ recurrent visual hallucinations that are well formed and detailed
  ▪ spontaneous features of parkinsonism, with onset subsequent to development of cognitive decline (rest tremor may be absent in DLB, but otherwise same classic features of Parkinson’s disease)
- suggestive/supportive features
  ▪ meets criteria for rapid eye movement (REM) sleep behavior disorder
  ▪ severe sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms)
  ▪ repeated falls, syncope, or transient episodes of unexplained loss of consciousness
  ▪ auditory or other nonvisual hallucinations, systematic delusions, and depression may also be present

Etiology and Pathogenesis
- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
- mixed DLB and AD pathology is common

Diagnostically Suggestive Markers
- low striatal dopamine transporter uptake on SPECT or PET
- relative preservation of medial temporal structures on CT/MRI

Epidemiology
- 0.1-5% of the general elderly population
- Lewy bodies are present in 20-35% of all dementia cases (more common in males)

Treatment
- acetylcholinesterase inhibitors (e.g. donepezil)

Prognosis
- average duration of survival 5-7 yr

Major or Mild Frontotemporal Neurocognitive Disorder
(formerly Frontotemporal Dementia)

Definition
- refers to a group of disorders caused by progressive cell degeneration in the brain's frontal or temporal lobes
- there are several variants of FTD each with specific core symptoms
- nevertheless, there is overlap between variants (i.e. NCD criteria along with relative sparing of learning and memory and perceptual-motor function)
- common neurocognitive symptoms include deficits in executive function (e.g. poor mental flexibility, abstract reasoning, response inhibition, planning/organization, and increased distractibility)
- "probable" is distinguished from "possible" frontotemporal NCD by:
  ▪ evidence of causative frontotemporal NCD genetic mutation, from either family history or genetic testing
  ▪ evidence of disproportionate frontal and/or anterior temporal atrophy on MRI or CT
  ▪ evidence of frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT
Behavioral Variant FTD
• most common variant; disinhibition and apathy are common symptoms
• insidious onset: must show progressive deterioration of behavior and/or cognition by observation or history
• prominent decline in social cognition and/or executive abilities
• typically early symptom presentation (i.e. within the first 3 yr)
• three out of the following symptoms must be present and persistent/recurrent
  ▪ behavioral disinhibition (socially inappropriate behavior, impulsive, careless)
  ▪ apathy or inertia
  ▪ loss of sympathy or empathy (diminished response to others’ needs/feelings, social interest)
  ▪ perseverative, stereotyped, or compulsive/ritualistic behavior
  ▪ hyperorality and dietary changes (binge eating, increased consumption of alcohol/cigarettes or inedible objects)

Language Variants (Primary Progressive Aphasia)
• prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension
• three subtypes
  ▪ nonfluent/agrammatic variant PPA (NFAV-PPA) or progressive nonfluent aphasia (PNFA): non-fluent, labored articulation/speech, anomia, preserved single word comprehension, word-finding deficit, impaired repetition
  ▪ semantic variant PPA (SV-PPA) or semantic dementia (SD): fluent, normal rate, anomia, impaired single word comprehension, intact repetition, use words of generalization (“thing”) or supraordinate categories (“animal” for “dog”)
  ▪ logopenic progressive aphasia (LPA): naming difficulty and impaired repetition

FTD Movement Disorders
• corticobasal degeneration (CBD): shakiness, lack of coordination, muscle rigidity and spasms
• progressive supranuclear palsy (PSP): walking and balance problems; frequent falls and muscle stiffness

Etiology and Pathogenesis
• unknown, however there is likely a genetic/familial component (40% have family history of early onset NCD)
• genetic variants: MAPT gene (Tau), PGRN gene (progranulin), VCP gene, TARDBP gene (TDP-43), CHMP2D gene
• unlike AD, FTD does not show amyloid plaques or neurofibrillary tangles, instead it is characterized by severe atrophy and specific neuronal inclusion bodies
• gross changes: atrophy in the frontal and anterior temporal lobes; cortical thinning; possible ventricular enlargement
• histological changes: gliosis, swollen neurons, microvacuolation, inclusion bodies in neurons/glia (Tau or TDP-43)

Epidemiology
• fourth most common cause of dementia (5% of all dementia cases)
• common cause of early-onset NCD in individuals younger than 65 yr

Prognosis
• median survival being 6-11 yr after symptoms onset and 3-4 yr after diagnosis
• survival is shorter and decline is faster than in typical Alzheimer’s disease

Major or Mild Vascular Neurocognitive Disorder
Definition
• diagnosis of major or mild NCD with determination of cerebrovascular disease as the dominant if not exclusive pathology that accounts for the cognitive deficits
• vascular etiology suggested by one of the following
  ▪ onset of cognitive deficits is temporally related to one or more cerebrovascular events
  ▪ evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function
  ▪ evidence of the presence of cerebrovascular disease from history, physical exam, and/or neuroimaging that is sufficient to account for the neurocognitive deficits
  ▪ neuroimaging evidence of cerebrovascular disease comprises one or more of the following
    ▪ one or more large vessel infarct or hemorrhage
    ▪ a strategically placed single infarct or hemorrhage (e.g. angular gyrus, thalamus, basal forebrain)
    ▪ two or more lacunar infarcts outside the brainstem
    ▪ extensive and confluent white matter lesions
• for mild vascular NCD: history of a single stroke or extensive white matter disease is sufficient
• for major vascular NCD: history of two or more strokes, a strategically placed stroke, or a combination of white matter disease, and one or more lacune is generally necessary
• associated features supporting diagnosis: personality and mood changes, abulia, depression, emotional lability, and psychomotor slowing

Etiology and Pathogenesis
• major risk factors are the same as those for cerebrovascular disease (i.e. HTN, DM, smoking, obesity, high cholesterol levels, high homocysteine levels, other risk factors for atherosclerosis, atrial fibrillation, and conditions increasing risk of cerebral emboli)
• major or mild vascular NCD with gradual onset and slow progression is generally due to small vessel disease leading to lesions in white matter, basal ganglia, and/or thalamus
• cognitive deficits can be attributed to disruption of cortical-subcortical circuits

Epidemiology
• second most common cause of NCD
• prevalence estimates for vascular dementia/NCD range from 0.2-13% (by age 70), 16% (ages 80+) to 44.6% (ages 90+)
• higher prevalence in African Americans compared to Caucasians and East Asians
• prevalence higher in males than in females

Creutzfeldt-Jakob Disease
• rare degenerative fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
• most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)
• investigations: CSF analysis, MRI brain (cortical and/or subcortical FLAIR changes), EEG (periodic complexes)
• definitive diagnosis is by brain biopsy
• no treatments currently exist

Normal Pressure Hydrocephalus
• see Neurosurgery, NS7

Aphasia

Definition
• an acquired disturbance of language characterized by errors in speech production, writing, comprehension, or reading

Neuroanatomy of Aphasia
• Broca's area (posterior inferior frontal lobe) involved in speech production (expressive)
• Wernicke's area (posterior superior temporal lobe) involved in comprehension of language (receptive)
• angular gyrus is responsible for relaying written visual stimuli to Wernicke's area for reading comprehension
• arcuate fasciculus association bundle connects Wernicke's and Broca's areas

Assessment of Language
• assessment of context
  • handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
• assessment of aphasia
  • spontaneous speech (fluency, paraphasias, repetition, naming, comprehension – auditory and reading, writing, neologisms)
### Apraxia

**Definition**
- Inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension, or inattention

**Clinicopathological Correlations**

**Table 16. Apraxia**

<table>
<thead>
<tr>
<th>Description</th>
<th>Tests</th>
<th>Hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideomotor</td>
<td>Blowing out a match; combing one's hair</td>
<td>Left</td>
</tr>
<tr>
<td>Ideational</td>
<td>Preparing and mailing an envelope</td>
<td>Right and left</td>
</tr>
<tr>
<td>Constructional*</td>
<td>Copying a figure</td>
<td>Right and left</td>
</tr>
<tr>
<td>Dressing*</td>
<td>Dressing</td>
<td>Right</td>
</tr>
</tbody>
</table>

*Refers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks.

### Agnosia

**Definition**
- Disorder in the recognition of the significance of sensory stimuli in the presence of intact sensation and naming

**Clinicopathological Correlations**

**Table 17. Agnosias**

<table>
<thead>
<tr>
<th>Description</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aperceptive Visual Agnosia</td>
<td>Bilateral temporo-occipital cortex</td>
</tr>
<tr>
<td>Associative Visual Agnosia</td>
<td>Bilateral inferior temporo-occipital junction</td>
</tr>
<tr>
<td>Prosopagnosia</td>
<td>Bilateral occipitotemporal areas or right inferior temporo-occipital region</td>
</tr>
<tr>
<td>Color Agnosia</td>
<td>Bilateral inferotemporal lesions</td>
</tr>
<tr>
<td>Impaired Stereognosia</td>
<td>Anterior parietal lobe in the hemisphere opposite the affected hand</td>
</tr>
<tr>
<td>Finger Agnosia</td>
<td>Dominant hemisphere parietal-occipital lesions</td>
</tr>
</tbody>
</table>

**Parietal Lobe Lesions**
- Lesions of the dominant parietal lobe are characterized by Gerstmann’s syndrome: acalculia, agraphesthesia, finger agnosia, and left-right disorientation
- Lesions of the non-dominant parietal lobe are characterized by neglect, anosognosia, and asomatognosia
- Cortical sensory loss (graphesthesias, astereognosia, impaired 2-point discrimination and extinction) can be seen with left or right parietal lesions
Mild Traumatic Brain Injury

Definition
- mild TBI = concussion
- trauma induced transient alteration in mental status that may involve loss of consciousness
- hallmarks of concussion: confusion and amnesia, which may occur within minutes
- loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h

Epidemiology
- 75% of TBIs are estimated to be mild; remainder are moderate or severe (see Neurosurgery, NS31 and Emergency Medicine, ER7)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features
- impairments following mild TBI
  - somatic: headache, sleep disturbance, N/V, blurred vision
  - cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
  - emotion and behavior: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
- associated conditions: brain contusion, diffuse axonal injury, C-spine injury

Investigations
- neuro exam to identify focal neurologic deficits
- neurocognitive assessment
  - simple orientation questions are inadequate to detect cognitive changes
  - initial assessment of severity is determined by
    - Glasgow Coma Scale: mild: 13-15, moderate: 9-12, severe: 3-8
    - sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool
- neuroimaging
  - x-ray of skull: not indicated for routine evaluation of MTBI
  - CT head as indicated (see Emergency Medicine, ER8)
  - MRI not indicated in initial evaluation – indicated in presence of continued or worsening symptoms despite normal CT

Treatment
- observation for first 24 h after mild TBI in all patients because of risk of intracranial complications
- emergency department for assessment if any loss of consciousness or persistent symptoms
- hospitalization with normal CT if GCS <15, seizures, or bleeding diathesis; or abnormal CT scan
- early rehabilitation to maximize outcomes
  - OT, PT, SLP, vestibular therapy, driving, therapeutic recreation
- pharmacological management of headaches, pain, depression
  - CBT, relaxation therapy
- follow Return to Play guidelines (www.thinkfirst.ca)

Prognosis
- most recover from mild TBI with minimal treatment, but some experience long-term consequences
- athletes with a previous concussion are at increased risk of subsequent concussion and cumulative brain injury
- repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
- sequelae include
  - postconcussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within weeks to months)
  - post-traumatic headaches: begin within seven days of injury
  - post-traumatic epilepsy: twofold increase in risk of epilepsy in 5 yr post-TBI, prophylactic anticonvulsants not effective
  - post-traumatic vertigo
### Neuro-Oncology

#### Paraneoplastic Syndromes
- see Endocrinology, E51

#### Tumors of the Nervous System
- see Neurosurgery, NS10

### Movement Disorders

#### Overview of Movement Disorders

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>Subjective restlessness relieved by stereotypic movements (e.g. squirming)</td>
</tr>
<tr>
<td>Asterixis</td>
<td>Loss of muscle contraction (negative myoclonus)</td>
</tr>
<tr>
<td>Athetosis</td>
<td>Slow writhing movements, especially distally</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Slow and/or small amplitude movements</td>
</tr>
<tr>
<td>Chorea</td>
<td>Brief, abrupt, irregular movements; can appear purposeful in milder forms</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>Any sudden involuntary movement, but the term is often used to describe the stereotypical movements that come with long-term neuroleptic or dopaminergic use</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Co-contraction of agonist and antagonists causing sustained twisting movements</td>
</tr>
<tr>
<td>Freezing</td>
<td>Episodes of halted motor action, especially during walking</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>Unilateral violent flinging movement</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Brief muscle group contraction that is either focal, segmental, or generalized</td>
</tr>
<tr>
<td>Myokimia</td>
<td>Spontaneous, fine, fascicular contraction of muscle</td>
</tr>
<tr>
<td>Tachykinses</td>
<td>Acceleration of movements</td>
</tr>
<tr>
<td>Tics</td>
<td>Stereotyped repetitive actions due to inner urge; can be suppressed</td>
</tr>
<tr>
<td>Tremor</td>
<td>Rhythmic alternating muscle contraction and relaxation</td>
</tr>
</tbody>
</table>

#### Function of the Basal Ganglia

- the cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, which then activate two pathways: direct and indirect
  - direct: cortex → striatum → GPi/SNr → thalamus → motor cortex
    - activation of this pathway removes the inhibitory effect of the GPi on the thalamus, letting the thalamus activate the cortex and ultimately allowing movement
  - indirect: cortex → striatum → GPe → STN → GPi/SNr → thalamus → motor cortex
    - activation of this pathway causes inhibition of the thalamus and ultimately prevents movement
Figure 20. Neural connections of the basal ganglia

Figure 21. Horizontal section of basal ganglia

**Movement Disorders**

**Differential Diagnoses**

1. Tremor
   - **Postural**: physiologic, anxiety, sedative/alcohol withdrawal, drug toxicity, heavy metal poisoning, carbon monoxide poisoning, thyrotoxicosis, benign essential tremor, cerebellar, Wilson's disease
     - benign essential tremor is a common autosomal dominant trait that presents as a bilateral postural tremor of the vertical axis, especially in the upper extremities
   - **Intention**: brainstem lesion, cerebellar lesion, alcohol, anticonvulsants, sedatives, Wilson's disease
   - **Resting**: Parkinsonism, Wilson's disease, mercury poisoning

In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson's disease), and CT/MRI (cerebellar disease) as indicated by type of tremor

**Alcohol**
- Dampens essential tremor
- Potentiates intention tremor
- Does not improve resting tremor of PD

>90% of essential tremor does not need treatment
Table 19. Approach to Tremors

<table>
<thead>
<tr>
<th>Resting</th>
<th>Postural</th>
<th>Intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Part</td>
<td>Distal UE</td>
<td>UE/head/voice</td>
</tr>
<tr>
<td>Characteristics</td>
<td>3-7 Hz pill rolling</td>
<td>6-12 Hz fine tremor</td>
</tr>
<tr>
<td>Worse with</td>
<td>Rest while concentrating</td>
<td>Sustained posture (outstretched arms)</td>
</tr>
<tr>
<td>Associated Sx</td>
<td>“TRAP”</td>
<td>± Autosomal dominant FHx</td>
</tr>
<tr>
<td>DDx</td>
<td>PD, Parkinson’s, Wilson’s disease</td>
<td>Physiologic, benign essential, drugs, hyperthyroid, hyperglycemic</td>
</tr>
<tr>
<td>Treatment</td>
<td>Sinemet, surgery, DBS</td>
<td>Propranolol, anticonvulsants, primidone</td>
</tr>
</tbody>
</table>

2. Chorea: Huntington’s disease, neuroacanthocytosis, SLE, APLA syndrome, Wilson’s disease, cerebrovascular disease, tardive dyskinesia, senile chorea, Sydenham’s chorea, pregnancy chorea

3. Dystonia
   - primary dystonia: familial, sporadic (torticollis, blepharospasm, writer’s cramp)
   - dystonia-plus syndromes: dopa-responsive dystonia, myoclonus-dystonia
   - secondary dystonia: thalamotomy, stroke, CNS tumor, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
   - heterodegenerative dystonias: Parkinsonian disorders, Wilson’s disease, Huntington’s disease

4. Myoclonus
   - physiologic myoclonus: hiccups, nocturnal myoclonus
   - essential myoclonus
   - epileptic myoclonus
   - symptomatic myoclonus
     - degenerative disorders (Wilson’s disease, Huntington’s disease, Corticobasal degeneration)
     - infectious disorders (CJD, viral encephalitis, AIDS-dementia complex)
     - metabolic disorders (drug intoxication/withdrawal, hypoglycemia, hyponatremia, HONK, hepatic encephalopathy, uremia, hypoxia)
     - focal brain damage (head injury, stroke, mass)

5. Tics
   - primary tic disorders: transient tic disorder, chronic tic disorder, Gilles de la Tourette, adult onset or senile
   - secondary tic disorders: encephalitis, CJD, Sydenham’s chorea, head trauma, drugs, mental retardation syndromes
   - association with OCD and ADHD

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**Parkinson’s Disease**

**Etiology**
- sporadic: combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- familial (10%): autosomal dominant α-synuclein mutations, autosomal recessive Parkin gene or DJ-1 gene mutation (juvenile onset)
- MPTP (neurotoxin)

**Epidemiology**
- prevalence of 0.3% in industrialized countries, but rises with increased age
- second most common neuro-degenerative disorder, after Alzheimer’s
- mean age of onset is 60 yr

**Risk Factors**
- family history, male, head injury, rural living, exposure to certain neurotoxins
- protective: coffee drinking, smoking, NSAID use, estrogen replacement in post-menopausal women

**Pathophysiology**
- loss of dopaminergic neurons in pars compacta of substantia nigra, thus reduced dopamine in striatum leading to disinhibition of the indirect pathway and decreased activation of the direct pathway causing increased inhibition of cortical motor areas
- α-synucleinopathy: α-synuclein accumulates in Lewy bodies and causes neurotoxicity in substantia nigra

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Most common cause of chorea is drug therapy for PD

Palatal myoclonus can result from lesion to the Dentato-Rubro-Olivary tract, and is associated with an audible clicking

Key Parkinsonian Features
- TRAP
  - Tremor (resting)
  - Rigidity
  - Akinesia/bradykinesia
  - Postural instability

Diagnostic Criteria
- Bradykinesia, plus one of: resting tremor, muscle rigidity, postural instability not caused by other factors, OR
- 3 or more of the following features:
  - Resting tremor
  - Unilateral onset
  - Persistent asymmetry, with side of onset most affected
  - Progressive disorder
  - Excellent response (70-100%) to levodopa
  - Severe levodopa-induced chorea
  - Response to levodopa for 5 or more yr
  - Clinical course lasting 10 or more yr
**Signs and Symptoms**
- positive motor
  - resting tremor: asymmetric 4-5 Hz “pill-rolling” tremor, especially in hands
  - rigidity: lead-pipe rigidity with cogwheeling due to superimposed tremor
- negative motor
  - bradykinesia: slow, small amplitude movements, fatiguing of rapid alternating movements, difficulty initiating movement
- related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
- freezing: occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds
- postural instability: late finding presenting as falls, festinating gait
- cognition: bradyphrenia (slow to think/respond), dementia (late finding)
- behavioral: decreased spontaneous speech, depression, sleep disturbances, anxiety
- autonomic: constipation, urinary retention, sexual dysfunction, later findings of orthostatic hypotension

**Etiology and Pathogenesis**
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway and decreased activity of the indirect pathway
- genetics: autosomal dominant CAG repeats (with anticipation) in Huntington gene on Chromosome 4, which leads to accumulation of defective protein in neurons
- treatment of early PD: dopamine agonists, amantadine, MAOI, COMT inhibitors
- surgical: thalamotomy, pallidotomy, deep brain stimulation (thalamic, pallidal, subthalamic)
- psychiatric (see Psychiatry, PS18)

**Other Parkinsonian Disorders**
- Dementia/NCD with Lewy bodies (DLB) (see Behavioral Neurology, N23)
- Progressive supranuclear palsy (PSP): tauopathy with limited vertical gaze (classically downgaze), early falls, axial rigidity and akinesia, dysarthria, and dysphagia
- Corticobasal degeneration (CBD): tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia ± “alien limbs” phenomenon; may also present as progressive non-fluent aphasia
- Multiple system atrophy (MSA): synucleinopathy presenting as either cerebellar predominant (previously olivo-ponto cerebellar atrophy or OPCA) or parkinsonism predominant (previously striato-nigral degeneration); both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- Vascular parkinsonism: multi-infarct presentation with lower body parkinsonism

**Huntington’s Disease**

**Etiology and Pathogenesis**
- genetics: autosomal dominant CAG repeats (with anticipation) in Huntington gene on Chromosome 4, which leads to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway and decreased activity of the indirect pathway

**Epidemiology**
- North American prevalence 4-8/100,000
- mean age of onset 35-44 yr; but varies with degree of anticipation from 5-70 yr

**Signs and Symptoms**
- typical progression: insidious onset with clumsiness, fidgetiness, and irritability, progressing over 15 yr to frank dementia, psychosis, and chorea
  - dementia: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parakinesia (pseudopurposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence
Investigations
- MRI: enlarged ventricles, atrophy of cerebral cortex and caudate nucleus
- genetic testing
  - expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene
  - CAG repeats on chromosome 4p16.3 that encodes the protein huntingtin

Treatment
- no disease altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin

Dystonia

Epidemiology
- third most common movement disorder after Parkinson's disease and essential tremor

Clinical Features
- symptoms exacerbated by fatigue, stress, emotions; relieved by sleep or specific tactile/proprioceptive stimuli ('geste antagoniste', e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalize if younger onset or leg dystonia

Treatment
- local medical: botulinum toxin
- systemic medical: anticholinergics (benztropine), muscle relaxants (baclofen), benzodiazepines, antidopaminergics (reserpine, neuroleptics); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotaxic thalamotomy (unilateral dystonia), posteroverentral pallidotomy

Tic Disorders

Definition
- a tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
- common criteria
  - tics may wax and wane in frequency but have persisted for an extended period of time
  - onset before age 18 yr
  - disturbance is not attributable to the physiological effects of a substance or another medical condition

Clinical Classification
- **Tourette's disorder**: multiple motor and one or more vocal tics that have persisted for more than 1 yr since onset
- **Persistent (chronic) motor or vocal tic disorder**: single or multiple motor or vocal tics (but not both motor and vocal) that have persisted for more than 1 yr since onset
- **Provisional tic disorder**: single or multiple motor and/or vocal tics present for <1 yr since first tic onset
- **other specified or unspecified tic disorder**: symptoms characteristic of a tic disorder but do not meet full criteria

Motor vs. Vocal Tics
- simple tics tend to be of short duration (milliseconds)
- complex tics tend to be longer (seconds) and often include a combination of simple tics
  - complex tics may often appear to be purposeful
- motor tics
  - simple: blinking, head jerking, shoulder shrugging, extension of the extremities
  - dystonic: bruxism, grinding teeth, abdominal tension, sustained mouth opening
- complex: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
- vocal tics
  - simple: blowing, coughing, grunting, throat clearing
  - complex: coprolalia (shout obscenities), echolalia (repeat others’ phrases), palilalia (repeat own phrases)

Treatment
- dopamine blocker
Tourette’s Syndrome
(Gilles de la Tourette’s Syndrome)

Definition According to DSM 5
1. presence of both multiple motor and one or more vocal tics at some point during the illness, although not necessarily concurrently
2. tics may wax and wane in frequency but have persisted for more than 1 yr since first tic onset (with no tic-free periods greater than 3 mo)
3. onset is before age 18 yr
4. not due to effect of a substance or another medical condition

Epidemiology
- estimated prevalence among adolescents 3-8 per 1,000 school-age children; M:F = 2:1 to 4:1

Signs and Symptoms
- tics: wide variety that wax and wane in type and severity; can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
  - can be worsened by anxiety, excitement, and exhaustion; better during calm focused activities
- psychiatric: compulsive behaviors (associated with OCD and ADHD), hyperactive behavior, rages, sleep-wake disturbances, learning disabilities

Treatment
- clonidine, clonazepam

Prognosis
- typically begins between ages 4-6
- peak severity occurs between ages 10-12, with a decline in severity during adolescence (50% are tic-free by 18 yr of age)
- tic symptoms however can manifest similarly in all age groups and across the lifespan

Cerebellar Disorders

Clinico-Anatomic Correlations
- vermis: trunk/gait ataxia
- cerebellar lobe (i.e. lateral): rebound phenomenon, scanning dysarthria, dysdiadochokinesis, dysmetria, nystagmus

Symptoms and Signs of Cerebellar Dysfunction
- nystagmus: observe during extraocular movement testing (most common is gaze-evoked nystagmus)
- dysarthria (ataxic): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/slurred speech on spontaneous speech (see CN X Vagus Nerve, N11)
- ataxia: broad-based, uncoordinated, lurching gait
- dysmetria: irregular placement of voluntary limb or ocular movement
- dysdiadochokinesis: impairment of rapid alternating movements (e.g. pronation – supination task)
- postural instability: truncal ataxia on sitting, titubation (rhythmic rocking of trunk and head), difficulty with tandem and broad-based gait
- intention tremor: typically orthogonal to intended movement, and increases as target is approached
- hypotonia: decreased resistance to passive muscular extension (occurs shortly after injury to lateral cerebellum)
- pendular patellar reflex: knee reflex causes pendular motion of leg (occurs after injury to cerebellar hemispheres)
- rebound phenomenon: overcorrection after displacement of a limb
- hypometric and hypermetric saccades
  - pendular reflexes at triceps

Wernicke-Korsakoff Syndrome

- see Psychiatry, PS23
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy
Cerebellar Ataxias

Congenital Ataxias
- early onset nonprogressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

Hereditary Ataxias
- autosomal recessive: includes Friedrich's ataxia, ataxia telangiectasia, vitamin E deficiency
  - Friedrich’s ataxia: prevalence 2/100,000; onset between 8 and 15 yr
    - signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration, dysarthria
    - death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- autosomal dominant: most commonly spinocerebellar ataxias (30 types, most due to CAG repeats)
  - signs: ataxia and dysarthria; ± myoclonus, chorea, polynuropathy, pyramidal or extrapyramidal features, hyporeflexia, seizures, dementia

Acquired Ataxias
- neurodegeneration (e.g. multiple system atrophy)
- systemic: alcohol, celiac sprue, hypothyroidism, Wilson’s, thiamine deficiency
- toxins: carbon monoxide, heavy metals, lithium, anticonvulsants, solvents
- vascular: infarct, bleed, basilar migraine
- autoimmune: MS, Miller-Fischer (GBS)

Vertigo
- see Otolaryngology, OT12

Gait Disturbances

Approach to Gait Disturbances
1. Characterization of the gait disturbance
   - posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, elaborate/inconsistent movements, standing from sitting
2. Identification of accompanying neurologic signs
   - full neurological exam required (diagnosis often can be made by P/E alone)
3. Identify red flags
   - sudden onset, cerebellar ataxia, paresis (hemi, para, or quadra), bowel/bladder incontinence
4. Workup
   - based on etiology – requires blood work, neuroimaging, and urgent neurologist referral

Table 20. Types of Gait Disturbance

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Loss</td>
<td>Broad based gait with tentative steps</td>
<td>Cataract surgery without lens replacement</td>
</tr>
<tr>
<td>Proprioceptive Loss</td>
<td>Sensory ataxia: wide-based with high stepping posture and positive Romberg</td>
<td>Demyelinating neuropathies, paraneoplastic syndrome, tabes dorsalis, MS, compressive myelopathy, B12 deficiency</td>
</tr>
<tr>
<td>Peripheral Nerve Disorder</td>
<td>1. Foot drop 2. Lumbosacral radiculopathy</td>
<td>Steppage gait, Acquired/hereditary peripheral neuropathy, compressive peroneal neuropathy, L4-5 radiculopathy</td>
</tr>
<tr>
<td>Myopathies</td>
<td>Waddling gait: broad based, short stepped gait with pronounced lumbar lordosis, rotation of pelvis</td>
<td>Progressive muscular dystrophy</td>
</tr>
<tr>
<td>Pyramidal/Corticospinal Tract Lesion</td>
<td>Spastic gait: spastic foot drop, circumduction, scissoring of legs or toe walking with bilateral circumduction</td>
<td>Unilateral: stroke (ischemic/hemorrhagic) Bilateral: cervical spondylosis, cerebral palsy, spinal cord tumor, combined spinal cord degeneration, MS, motor neuron disease</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>1. Parkinsonian gait: small paces, stooped posture, reduced armswing 2. Choreic/hemiballistic/dystonic gait</td>
<td>Infarct, Huntington’s, Sydenham’s chorea, Wilson’s disease, SLE, neuroleptic medications, polycythemia vera, genetic dystonia</td>
</tr>
<tr>
<td>Cerebellar Disorder</td>
<td>Cerebellar ataxic gait: wide-based without high stepping; veers to side of lesion Alcoholic gait</td>
<td>Primary and secondary neoplasm, toxins (alcohol), vit E deficiency, hypothyroid, hypoxia, hypoglycemia, paraneoplastic syndrome</td>
</tr>
</tbody>
</table>

Central Motor Systems
- 3 components to the control of gait:
  - Pyramidal: main outflow from cortex to spinal cord
  - Extrapyramidal: basal ganglia inhibits excess movements
  - Cerebellum: affects coordination of gait
Motor Neuron Disease

Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease)

Definition
- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal

Etiology
- idiopathic (most), genetic (5-10% familial, especially SOD1 mutation, other: C9orf72, TARDBP)

Pathology
- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

Epidemiology
- 5/100,000; incidence increases with age

Signs and Symptoms
- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms
- bulbar findings: dysarthria (flaccid or spastic), dysphagia, tongue atrophy and fasciculations, facial weakness and atrophy
- pseudobulbar affect, frontotemporal dementia (up to 10%)
- sparing of sensation, ocular muscles, and sphincters

Investigations
- EMG: chronic denervation and reinnervation, fasciculations
- NCS: to rule out peripheral neuropathy (i.e. multifocal motor neuropathy with conduction block)
- CT/MRI: to rule out cord disease/compression

Management
- riluzole (modestly slows disease progression)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine, regular exercise, and physical therapy
  - sialorrhea: TCA (i.e. amitriptyline), sublingual atropine drops, parotid/submandibular botox (rare)
  - pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
  - non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (i.e. PEG tube), rehabilitation (PT, OT, SLP), psychosocial support

Prognosis
- median survival 3 yr; death due to respiratory failure

Other Motor Neuron Diseases

- degenerative
  - progressive muscular atrophy (progressive bulbar palsy): only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centers
  - primary lateral sclerosis (progressive pseudobulbar palsy): UMN symptoms, later onset, not fatal with variable disability; 5-10% of patients in ALS centers
  - spinal muscular atrophy: pediatric disease with symmetric LMN symptoms
- infectious
  - post-polio syndrome: residual asymmetric muscle weakness, atrophy
- acquired
  - multifocal motor neuropathy: conduction block on NCS, asymmetric LMN symptoms, ± anti-GM1 Ab, treatable with IVIg

Peripheral Neuropathies

Diagnostic Approach to Peripheral Neuropathies
1. Differentiate: motor vs. sensory vs. autonomic vs. mixed
2. Pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; cranial nerve involvement
3. Temporal pattern: acute vs. chronic; relapsing/remitting vs. constant vs. progressive
4. History: PMH, detailed FHx, exposures (e.g. insects, toxins, sexual, travel), systemic symptoms
5. Detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status
Classification
- monoradiculopathy: dermatomal deficit due to single nerve root lesion
  - due to disc herniation or root compression causing radicular pain
  - little tactile anesthesia, as dermatomes overlap
- polyradiculopathy: multiple dermatome deficits due to multiple nerve root lesions
  - one type is cauda equina syndrome (lumbosacral roots)
- plexopathy: deficit matching distribution of a nerve plexus
  - brachial plexopathy
    - upper (C5-C7): LMN sx of shoulder and upper arm muscles (Erb’s palsy)
    - lower (C8-T1): LMN sx and sensory sx of forearm and hand (Klumpke’s palsy)
  - DDx: trauma, idiopathic neuritis, tumor infiltration, radiation, thoracic outlet syndrome
    (i.e. cervical rib)
- lumbosacral plexopathy (rare, especially unilateral)
  - DDx: idiopathic neuritis, infarction (i.e. DM), compression
- mononeuropathy: single nerve deficit
  - carpal tunnel syndrome (most common): compression of median nerve at wrist
    - symptoms: wrist pain, paresthesia first 3 and ½ digits, ± radiation to elbow, worse at night
    - signs: Tinel’s sign, Phalen’s test, thenar muscle wasting, sensory deficit
    - EMG and NCS: slowing at wrist (both motor and sensory)
  - Bell’s palsy (most common cranial neuropathy): see Otolaryngology, OT23
    - other less common mononeuropathies due to entrapment/compression: ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)
- mononeuropathy multiplex: deficit affecting multiple discrete nerves (asymmetric)
  - must rule out vasculitis or collagen vascular disease
- polyneuropathy: symmetrical distal stocking-glove pattern
  - symmetrical distal sensorimotor deficit affecting longest fibers first (stocking-glove distribution), hypotonia; progression of dysesthesia early and weakness later
  - etiology: DM (most common), renal disease, substances, toxins, genetics, SLE, HIV, leprosy, alcohol, B12 deficiency, uremia
- chronic inflammatory demyelinating polyneuropathy (CIDP)
  - chronic relapsing sensorimotor polyneuropathy with increase in protein in CSF and demyelination (shown on EMG/NCS)
  - course is fluctuating, in contrast with the acute onset of GBS
  - treatment: first-line is prednisone; alternatives are plasmapheresis, IVIg, and azathioprine

Table 21. Differential Diagnosis of Symmetric Polyneuropathy

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Mechanism</th>
<th>Course</th>
<th>Modalities</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PAN</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatol. RH19</td>
</tr>
<tr>
<td>SLE</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatol. RH11</td>
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<td>RA</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatol. RH8</td>
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<tr>
<td>Infectious</td>
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<td></td>
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<tr>
<td>HIV</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/A</td>
<td>HIV serology</td>
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<tr>
<td>Leprosy</td>
<td>Infiltrative</td>
<td>Chronic</td>
<td>S/A</td>
<td>Leprosy serology</td>
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<td>Lyme</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>M</td>
<td>Nerve biopsy</td>
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<td>Lyme serology</td>
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<tr>
<td>Immune</td>
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<tr>
<td>GBS</td>
<td>Demyelination</td>
<td>Acute</td>
<td>M</td>
<td>LP († protein; no † cells)</td>
</tr>
<tr>
<td>CIDP</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>LP († protein)</td>
</tr>
<tr>
<td>Hereditary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HMSN</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Paraneoplastic antibodies</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>SPEP</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Axonal</td>
<td>Chronic</td>
<td>M</td>
<td>Skeletal bone survey</td>
</tr>
<tr>
<td>Lymphoma biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monoclonal</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>SPEP</td>
</tr>
<tr>
<td>gammapathy</td>
<td></td>
<td></td>
<td></td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>Toxic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EtOH</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>GGT, MCV</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>Urine heavy metals</td>
</tr>
<tr>
<td>Medications</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>Drug levels</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>Ischemic/axonal</td>
<td>Chronic</td>
<td>S/A</td>
<td>Fasting glucose, HbA1c, 2 h OGTT</td>
</tr>
<tr>
<td>Hyperthyroidm</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/M</td>
<td>TSH, T3, T4</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/A</td>
<td>Electrolytes, Cr, BUN</td>
</tr>
<tr>
<td>Nutritional</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B12 deficiency</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>Vitamin B12</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>M</td>
<td>Urine porphyrins</td>
</tr>
<tr>
<td>Amyloid</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S</td>
<td>Nerve biopsy</td>
</tr>
</tbody>
</table>

A = autonomic; CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; GGT = gamma-glutamyl transferase; HMSN = hereditary motor sensory neuropathy; M = motor; GBS = Guillain-Barre syndrome; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; S = sensory; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis; TSH = thyroid stimulating hormone; T3, T4 = thyroid hormones.
Guillain-Barré Syndrome

- **definition**: acute rapidly evolving demyelinating inflammatory polyneuropathy that often starts in the distal lower limbs and ascends
- **etiology**
  - autoimmune attack and damage to peripheral nerve myelin
  - sometimes preceded by viral/bacterial infections
- **signs and symptoms**
  - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
  - motor: weakness starting distally in legs, areflexia
  - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- **investigations**
  - CSF: albuminocytological dissociation (high protein, normal WBC)
  - EMG/NCS: conduction block, differential or focal (motor > sensory) slowing, decreased F-wave, sural sparing
- **subtypes**
  1. acute inflammatory demyelinating polyneuropathy (AIDP)
  2. acute motor-sensory axonal neuropathy (AMSAN)
  3. acute motor axonal neuropathy (AMAN)
- **treatment**
  - IVIg or plasmapheresis, ± pain management, monitor vitals and vital capacity
- **prognosis**
  - peak of symptoms at 2-3 wk, resolution at 4-6 wk
  - 5% mortality (higher if require ICU); up to 15% have permanent deficits

**Neuromuscular Junction Diseases**

**Clinical Approach to Disorders of the Neuromuscular Junction**

**Table 22. Common Disorders of the Neuromuscular Junction**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Myasthenia Gravis</th>
<th>Lambert-Eaton</th>
<th>Botulism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular/Bulbar Paresis</td>
<td>+</td>
<td>–</td>
<td>+ (early)</td>
</tr>
<tr>
<td>Limb Weakness</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fatiguability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Post-Exercise Enhancement</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reflexes</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Anticholinergic Sx</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sensory Sx</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Associated Conditions</td>
<td>Thymoma</td>
<td>Small cell carcinoma</td>
<td>GI S&amp;S</td>
</tr>
<tr>
<td>Repetitive EMG Stimulation</td>
<td>Decremental response</td>
<td>Incremental response</td>
<td>↑ (rapid stimulation) ↓ (slow stimulation)</td>
</tr>
</tbody>
</table>

**Myasthenia Gravis**

**Etiology and Pathophysiology**
- progressive autoimmune disorder due to anti-AChR antibodies, resulting in early saturation at the NMJ and inadequate muscle activation with increasing nerve stimulation
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia

**Epidemiology**
- bimodal age of onset – 20s (mostly women) and 60s (mostly men)

**Signs and Symptoms**
- see Table 22
- fatiguable, symmetric or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
- ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
- symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
- respiratory muscle weakness may lead to respiratory failure
Investigations
- edrophonium (Tensilon®) test
  - assess for improvement over 2 min following edrophonium injection
- EMG
  - repetitive stimulation → decremental response
  - single fiber electromyography shows increased jitter (80-100% sensitivity)
- spirometry – forced vital capacity may be used to monitor adequacy of respiratory effort over time
- anti-acetylcholine receptor antibody assay (70-80% sensitivity)
- MUSK antibody may be used if seronegative for AChR antibody
- CT/MRI to screen for thymoma/thymic hyperplasia

Treatment
- thymectomy
  - 85% of patients show improvement or remission
- symptomatic relief
  - acetylcholinesterase inhibitors (e.g. pyridostigmine)
    - does not affect primary pathologic process so rarely results in control of disease when used alone
- immunosuppression
  - steroids are mainstay of treatment (70-80% remission rate)
- azathioprine, cyclophosphamide, and mycophenolate as adjuncts or as steroid sparing therapy
- short-term immunomodulation (for crises)
  - IVIg and plasmapheresis

Prognosis
- 30% eventual spontaneous remission
- with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

Lambert-Eaton Myasthenic Syndrome

Etiology and Pathophysiology
- autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased ACh release at the NMJ
- 50-66% are associated with small cell carcinoma of the lung

Signs and Symptoms
- see Table 22
- weakness of skeletal muscles without sensory or coordination abnormalities
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and ocular muscles affected in 25% (vs. 90% in MG)
- prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

Investigations
- edrophonium test (see Myasthenia Gravis, N37) → no response
- EMG
  - rapid (>10 Hz) repetitive stimulation → incremental response
  - post-exercise facilitation → an incremental response with exercise
- screen for malignancy, especially small cell lung cancer

Treatment
- tumor removal
- acetylcholine modulation
  - increased acetylcholine release (3,4-diaminopyridine)
  - decreased acetylcholine degradation (pyridostigmine)
- immunomodulation
  - steroids, plasmapheresis, IVIg

Botulism

Etiology and Pathophysiology
- caused by a toxin produced by spores of Clostridium botulinum bacteria, which is found in soil and water throughout the world
- bacteria can enter the body through wounds or by ingesting improperly preserved foods
- infantile botulism is the most common form, and is usually from ingestion of honey or corn syrup

Signs and Symptoms
- occur 6-48 h after ingestion
- difficulty with convergence, ptosis, paralysis of extraocular muscles
- dilated, poorly reactive pupils
• other autonomic dysfunction: jaw weakness, dysarthria, dysphagia
• spreads to trunk and limbs
  ▪ abdominal cramps with N/V
  ▪ symmetric weakness with paralysis and absent/decreased deep tendon reflexes
• anticholinergic symptoms: dry mouth, constipation, urinary retention
• rarely respiratory distress, potentially advancing to respiratory failure
  ▪ pattern of paresis often starts with GI symptoms (constipation, early satiety), then paresis of
  extracocular muscles, then dysphagia, then limbs/respiratory involvement; all associated with
dry mouth

Investigations
• blood test for toxin
• stool culture

Treatment
• botulinum anti-toxin – good prognosis with prompt treatment
• supportive therapy as required

**Myopathies**

**Clinical Approach to Muscle Diseases**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Key Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory</strong></td>
<td>Myalgias</td>
<td>↑ CK</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Pharyngeal involvement</td>
<td>Biopsy: endomysial infiltrates; necrosis</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Myalgias, Characteristic rashes with Can be paraneoplastic</td>
<td>↑ CK</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>See Respirilogy, R14</td>
<td>Biopsy: perifascicular atrophy</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>Weak quadriceps and deep finger flexors</td>
<td>↑ CK</td>
</tr>
<tr>
<td></td>
<td>See Endocrinology, E20, E33</td>
<td>Biopsy: inclusion bodies</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Myalgias</td>
<td>↑ myoglobin</td>
</tr>
<tr>
<td>Thyroid (↑ or ↓)</td>
<td>See Endocrinology, E20, E33</td>
<td>TSH, serum cortisol, calcium panel</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Medication history</td>
<td>Toxicology screen</td>
</tr>
<tr>
<td>Parathyroid (↑ or ↓)</td>
<td>Medication or toxin history</td>
<td>Biopsy: selective loss of thick myosin filaments</td>
</tr>
<tr>
<td><strong>Toxic</strong></td>
<td>Medication history</td>
<td>Dystrophism analysis: absent</td>
</tr>
<tr>
<td>Critical illness myopathy</td>
<td>Hx steroids and nondepolarizing paralyzing agents</td>
<td>Dystrophism analysis: abnormal</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td>Myalgias</td>
<td>↑ myoglobin</td>
</tr>
<tr>
<td>Parasitic, bacterial, or viral</td>
<td>Failure to wean from ventilation</td>
<td>Myopathy</td>
</tr>
<tr>
<td><strong>Hereditary</strong></td>
<td>Myalgias</td>
<td>↑ myoglobin</td>
</tr>
<tr>
<td>Dystrophy</td>
<td>Inflammatory myopathy</td>
<td>MYOPATHY</td>
</tr>
<tr>
<td>Duchenne</td>
<td>Early onset (Duchenne and Becker)</td>
<td>Dystrophyns analysis: absent</td>
</tr>
<tr>
<td>Becker</td>
<td>Progressive proximal muscle weakness</td>
<td>Dystrophyns analysis: abnormal</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>Distal myopathy, Myotonia</td>
<td>Genetic testing</td>
</tr>
<tr>
<td><strong>Hereditary</strong></td>
<td>Exercise-related myalgias, cramping, and myoglobinuria</td>
<td>↑ lactate</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Myalgias</td>
<td>↑ serum/urinary myoglobin post-exercise</td>
</tr>
<tr>
<td>McArdle’s</td>
<td>Normal between attacks</td>
<td>Normal, ↑ or ↓ K⁺</td>
</tr>
<tr>
<td><strong>Hereditary</strong></td>
<td>Myoclonus, generalized seizures, dementia, myopathy</td>
<td>Biopsy: ragged red fibers</td>
</tr>
<tr>
<td>Periodic Paralysis</td>
<td>“Channelopathy”</td>
<td>Increased lactate</td>
</tr>
<tr>
<td>MERRF</td>
<td>Myoclonus, generalized seizures, dementia, myopathy</td>
<td>Biopsy: ragged red fibers</td>
</tr>
<tr>
<td>MELAS</td>
<td>Pediatric onset, stroke-like symptoms, episodic vomiting, dementia</td>
<td>Biopsy: lagged red fibers</td>
</tr>
<tr>
<td>Kearns Sayre</td>
<td>Progressive ophthalmoplegia, retinal pigment degeneration, cardiac conduction abnormalities</td>
<td>Biopsy: lagged red fibers</td>
</tr>
</tbody>
</table>

MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF = mitochondrial encephalomyopathy with ragged red fibers
**Polymyositis/Dermatomyositis**

- see **Rheumatology, RH15**

**Myotonic Dystrophy**

**Etiology and Pathophysiology**
- unstable trinucleotide (CTG) repeat in DMK gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms
- autosomal dominant

**Epidemiology**
- most common adult muscular dystrophy
- prevalence 3-5/100,000

**Signs and Symptoms**
- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance
- physical exam
  - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
  - myotonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
  - cardiac: 90% have conduction defects (1st heart block; atrial arrhythmias)
  - respiratory: hypoventilation 2nd to muscle weakness
  - ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
  - other: DM, infertility, testicular atrophy
- EMG: subclinical myotonia – long runs with declining frequency and amplitude

**Treatment and Prognosis**
- no cure, progressive, death usually around 50 yr
- management of myotonia: phenytoin

**Duchenne and Becker Muscular Dystrophy**

- see **Pediatrics, P45**

**Pain Syndromes**

**Approach to Pain Syndromes**

**Definitions**
- **nociceptive pain:** pain arising from normal activation of peripheral nociceptors
- **neuropathic pain:** pain arising from direct injury to neural tissue, bypassing nociceptive pathways
- **spontaneous pain:** unprovoked burning, shooting, or lancinating pain
- **paresthesiae:** spontaneous abnormal nonpainful sensations (e.g. tingling)
- **dysesthesiae:** evoked pain with inappropriate quality or excessive quantity
- **allodynia:** a dyesthetic response to a non-noxious stimulus
- **hyperalgesia:** an exaggerated pain response to a noxious stimulus

**Non-Pharmacological Management**
- physical (PT, acupuncture, chiropractic manipulation, massage)
- psychoeducational (CBT, family therapy, education, psychotherapy)

**Medical Pain Control**
- combination multi-modal therapy is important
- primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches, and arthritis), opiates
- adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympatholytics (phenoxymenzamine), α2-adrenergic agonists (clonidine)

**WHO Pain Ladder**
- **Mild Pain:** Non-opioid (acetaminophen and/or NSAID) ± adjuvant
- **Moderate Pain:** Opioid for mild to moderate pain (codeine/oxycodone) + non-opioid ± adjuvant
- **Severe Pain:** Opioid for moderate to severe pain (morphine/hydromorphone) + non-opioid ± adjuvant

**Axonal regeneration is directed by intact nerve sheaths; if the nerve sheath is damaged, axons grow without direction, become tangled and form a neuroma, which can result in ectopic electrical impulses and neuropathic pain**
Surgical Pain Control
- peripheral ablation: nerve blocks, facet joint denervation
- direct delivery: implantable morphine pump
- central ablation: stereotactic thalamotomy, spinal tractotomy, or dorsal root entry lesion
- DBS or dorsal column stimulation

Neuropathic Pain

Definition
- pain resulting from a disturbance of the central or peripheral nervous system

Symptoms and Signs
- hyperalgesia/allodynia
- subjectively described as burning, heat/cold, pricking, electric shock, perception of swelling, numbness (i.e. stocking/sock distribution)
- can be spontaneous or stimulus evoked
- distribution may not fall along classical neuro-anatomical lines
- associated issues: sleep difficulty, anxiety/stress/mood alteration

Causes of Neuropathic Pain
- sympathetic
- complex regional pain syndrome
- central: abnormal CNS activity
  - phantom limb, post spinal cord injury, post stroke, MS
- non-sympathetic: damage to peripheral nerves
- systemic disease: DM, thyroid disease, renal disease, rheumatoid arthritis
- nutritional/toxicity: alcoholism, pernicious anemia, chemotherapy
- infectious: post-herpetic, HIV
- trauma/compression: nerve entrapment, trigeminal neuralgia, post surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy

Treatment
- identify/treat underlying cause
- pharmacotherapy
  - anticonvulsant: pregabalin, gabapentin, sodium valproate
  - antidepressant: amitriptyline, venlafaxine, duloxetine
  - opioids: dextromethorphan, morphine sulphate, tramadol, oxycodone
  - other: capsaicin and isosorbide dinitrate spray
- common non-pharmacologic therapies
  - percutaneous electrical stimulation (moderate evidence)
  - neuropsychiatry: CBT, psychotherapy
  - rehabilitation: physiotherapy
- surgical therapies: dorsal column neurostimulator, DBS (thalamus)

Tic Douloureux (Trigeminal Neuralgia)

Clinical Features
- recurrent episodes of sudden onset, excruciating unilateral paroxysmal shooting "electric" pain in trigeminal root territory (V3>V2>V1)
- may have normal sensory exam
- pain lasts seconds/minutes over days/weeks; may remit for weeks/months
- triggers: touching face, eating, talking, cold wind, shaving, applying make-up

Etiology
- classic TN: idiopathic
- secondary TN: compression by tortuous blood vessel (superior cerebellar artery), cerebellopontine angle tumor (5%), MS (5%)

Epidemiology
- F>M; usually middle-aged and elderly

Diagnosis
- clinical diagnosis
- investigate for secondary causes, which are more likely if bilateral TN or associated sensory loss
  - MRI to rule out structural lesion, MS, or vascular lesion
Treatment
- first line: carbamazepine or oxcarbazepine
- second line: baclofen or lamotrigine
- narcotics not generally recommended
- if medical treatment fails: Gasserian ganglion percutaneous technique, gamma knife, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression

Postherpetic Neuralgia

Clinical Features
- pain persisting in the region of a cutaneous outbreak of herpes zoster
- constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
- distribution: thoracic, trigeminal, cervical > lumbar > sacral
- associated impaired sleep, decreased appetite, decreased libido

Etiology and Pathogenesis
- destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

Epidemiology
- incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
- risk factors: older age, greater acute pain, greater rash severity

Prevention
- varicella zoster vaccine in childhood reduces incidence of varicella zoster
- herpes zoster vaccine (Zostavax®) reduces incidences of shingles, PHN, and other herpetic sequel (currently recommended by the Centers for Disease Control and Prevention [CDC] for those >60 yr old)

Treatment
- medical: TCA (i.e. amitryptiline), anti-convulsants (i.e. pregabalin, gabapentin), analgesia (i.e. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  - early treatment of acute herpes zoster with antivirals (acyclovir; longer-acting famciclovir and valacyclovir more effective)
  - treatment of herpes zoster with corticosteroids DOES NOT decrease PHN
- surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus

Painful Diabetic Neuropathy

Approach
- determine if pain is neuropathic or vascular
- more likely neuropathic if
  - feet > calves
  - sharp/tingling pain
  - pain present at rest and improves with walking

Treatment
- Level A: pregabalin
- Level B: venlafaxine, duloxetine, amitryptiline, gabapentin, valproate, rarely opioids, capsaicin

Complex Regional Pain Syndromes

Clinical Features
- presence of an initiating noxious event (MI, stroke)
- continuing pain, allodynia, or hyperalgesia with pain disproportionate to inciting event
- evidence during the course of symptoms of edema, changes in skin blood flow or abnormal vasomotor activity
- absence of conditions that would otherwise account for degree of pain and dysfunction
- other features can include edema, osteoporosis, hyperhidrosis, hair loss, fascial thickening

Classification
- CRPS type I (reflex sympathetic dystrophy): minor injuries of limb or lesions in remote body areas precede onset of symptoms
- CRPS type II (causalgia): injury of peripheral nerves precedes the onset of symptoms
**Investigations**
- trial of differential neural blockade may be helpful in diagnosis
- autonomic testing (evidence of sympathetic dysfunction)
- bone scan, plain radiography, MRI

**Prevention**
- early mobilization after injury/infarction

**Treatment**
- goal of treatment: to facilitate function
- conservative treatment: education, support groups, PT/OT, smoking cessation
- medical: topical capsaicin, TCA, NSAID, tender point injections with corticosteroid/lidocaine, gabapentin/pregabalin/lamotrigine, calcitonin or bisphosphonates, oral corticosteroids
- surgical: paravertebral sympathetic ganglion blockade
- refer to pain management clinic

**Headache**

- see Emergency Medicine, ER24 and Family Medicine, FM34

**Clinical Approach**
- **history**
  - pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g. worse in AM, worse with bending/cough/Valsalva)
  - associated symptoms: visual changes, change in mental status, N/V, fever, meningismus, photophobia, phonophobia, TMJ popping/clicking, jaw claudication, neurological symptoms
  - precipitating/alleviating factors (triggering factors, analgesics), medications (especially nitrates, CCBs, NSAIDs, anticoagulants), PMH, FHx
  - red flags (possible indications for CT scan/further investigation): new-onset headache (especially if age <5 or >50), quality worse/different than previous headaches, sudden and severe (‘thunderclap’), immunocompromised, fever, focal neurological deficits, trauma
- **physical exam**
  - vitals (including BP and temp), Kernig’s/Brudzinski’s, MSK examination of head and neck
  - HEENT: fundi (papilledema, retinal hemorrhages), red eye, temporal artery tenderness, sinus palpation, TMJ
  - full neurological exam (including LOC, orientation, pupils (symmetry), and focal neurological deficits)
  - red flags: papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

**Classification**
- **primary**
  - tension, migraine, cluster, other autonomic cephalgias
- **secondary**
  - cervical OA, TMJ syndrome, SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN or pseudotumor cerebri), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-eclampsia, post LP, drugs/toxins (e.g. nitroglycerin use and analgesia withdrawal); all can be associated with serious morbidity or mortality

**Table 24. Headaches – Selected Primary Types**

<table>
<thead>
<tr>
<th></th>
<th>Tension-Type</th>
<th>Migraine</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalence</strong></td>
<td>70%</td>
<td>~10-20%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td>15–40</td>
<td>10–30</td>
<td>20–40</td>
</tr>
<tr>
<td><strong>Sex Bias</strong></td>
<td>F&gt;M</td>
<td>F&gt;M</td>
<td>M&gt;F</td>
</tr>
<tr>
<td><strong>Family History</strong></td>
<td>None</td>
<td>+ + +</td>
<td>+</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Bilateral frontal&lt;br&gt;Nuchal-occipital&lt;br&gt;Fronto-temporal&lt;br&gt;Retro-orbital</td>
<td>Unilateral &gt; bilateral&lt;br&gt;Fronto-temporal</td>
<td>Retro-orbital</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Minutes – days</td>
<td>Hours – days</td>
<td>10 min-2 h</td>
</tr>
<tr>
<td><strong>Onset/Course</strong></td>
<td>Gradual; worse in PM</td>
<td>Gradual; worse in PM</td>
<td>Daily attacks for weeks to months; more common early AM or late PM</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Band-like; constant</td>
<td>Throbbing</td>
<td>Constant, aching, stabbing</td>
</tr>
</tbody>
</table>
### Table 24. Headaches – Selected Primary Types (continued)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Tension-Type</th>
<th>Migraine</th>
<th>Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated Sx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AED</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Table 25. Prophylactic Management of Migraine Headaches

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Evidence</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Propranolol</td>
<td>A</td>
<td>Asthma, DM (mask</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Timolol</td>
<td>A</td>
<td>hypoglycemia)</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>B</td>
<td>CHF</td>
<td>Light-headedness</td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>A</td>
<td>Heart disease, glaucoma</td>
<td>Sedation</td>
</tr>
<tr>
<td></td>
<td>Nortriptyline</td>
<td>C</td>
<td><em>Avoid in elderly</em></td>
<td>Dry mouth</td>
</tr>
<tr>
<td>CCBs</td>
<td>Fluoxetine</td>
<td>A</td>
<td>Depression, obesity</td>
<td>Weight gain</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>B</td>
<td>Heart disease</td>
<td>Weight gain (10-20 lb), constipation</td>
</tr>
<tr>
<td>AED</td>
<td>Valproate</td>
<td>A</td>
<td>Liver, renal, pancreatic diseases</td>
<td>Weight gain, tremor, alopecia, tarantogenic: neural tube defect</td>
</tr>
<tr>
<td></td>
<td>Topiramate + folic acid supplement</td>
<td>A</td>
<td>Renal disease</td>
<td>Paresthesia, weight loss, cognitive: memory loss, difficulty concentrating, renal stone (rare)</td>
</tr>
</tbody>
</table>

### Table 26. Headaches – Selected Serious but Rare Secondary Types

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Meningeal Irritation</th>
<th>Increased ICP</th>
<th>Temporal Arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any age</td>
<td>Any age</td>
<td>&gt;60 yr</td>
<td></td>
</tr>
<tr>
<td>Generalized</td>
<td>Any location</td>
<td>Temporal</td>
<td></td>
</tr>
<tr>
<td>Meningitis: hours-days</td>
<td>Gradual; worse in AM</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>SAH: thunderclap onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Severe</td>
<td>Variable; can be severe</td>
<td></td>
</tr>
<tr>
<td>Provoking</td>
<td>Head movement</td>
<td>Lying down Valsalva Head low Exertion</td>
<td>Jaw claudication</td>
</tr>
<tr>
<td>Associated Sx</td>
<td>Neck stiffness</td>
<td>N/V</td>
<td>Polymyalgia rheumatica Visual loss</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
<td>Focal deficits (e.g. CN palsies)</td>
<td></td>
</tr>
<tr>
<td>Physical Signs</td>
<td>Kernig’s sign</td>
<td>Focal neural symptoms</td>
<td>Decreased level of consciousness</td>
</tr>
<tr>
<td></td>
<td>Brudzinski’s sign</td>
<td>Papilledema</td>
<td>Temporal artery changes:</td>
</tr>
<tr>
<td></td>
<td>Meningismus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>CT/MRI with gadolinium</td>
<td></td>
<td>Prednisone</td>
</tr>
<tr>
<td></td>
<td>LP; antibiotics for bacterial meningitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>Meningitis, SAH</td>
<td>Tumor, IHH, malignant HTN</td>
<td>Vasculitis (GCA)</td>
</tr>
</tbody>
</table>

IH = idiopathic intracranial hypertension

---

**The Rational Clinical Examination: Does this Patient with Headache have a Migraine or Need Neuroimaging?**

JAMA 2006;296:1274-1283

**Does this patient with headache have a migraine?**

The most useful panel of questions for diagnosing migraine is summarized by the POUNDing mnemonic:

- P – Pulsatile quality
- O – duration of 4-72 h
- U – Unilateral location
- N – Nauses or vomiting
- D – Distinguishing intensity

The LR for definite or possible migraine diagnosis varies with the number of features present: with >4, 3, and ≤2 features, the LRs are 24 (1.5-300), 3.5 (1.3-9.2), and 0.41 (0.32-0.52), respectively.

**Does this patient with headache need neuroimaging?**

In patients with new or changed headache the prevalence of significant intracranial pathology is 32% (24-42%), and in those presenting with thunderclap headache the prevalence is 43% (20-68%). Several individual clinical features were found to be predictive of significant intracranial pathology: Symptom

**Cluster-type headache**

10.7 (2.2-52)

**Abnormal neurological exam**

5.3 (2.4-12)

**Unidentified headache**

3.8 (2.071)

**Tension/migraine/cluster-type**

2.25 (NNT=3.9). Valproate and topiramate with NNH 7.0-18.8 are better than placebo, while clonazepam, acetazolamide, lamotrigine, and vigabatrin are not.

**Conclusion**

Anticonvulsants are effective in reducing migraine frequency and reasonably well-tolerated. Valproate and topiramate are the two most studied but further studies of head-to-head comparisons between agents is needed.

---

**Acute and Preventive Pharmacologic Treatment of Cluster Headache**

Neurology 2010;75:463-473

**Study**

Meta-analysis of prospective, double-blind, RCTs of pharmacologic agents for prevention or treatment of CH.

**Results**

27 trials were included. Sumatriptan 6 mg SC, zolmitriptan nasal spray 5-10 mg, and 100% oxygen 6-12 L/min received Level A recommendation for acute treatment. For prevention, Level B recommendations were given for intranasal cimamide 100 μg daily and subcuticular steroid injections.

**Conclusion**

Sumatriptan, zolmitriptan, and mid flow oxygen are effective acute treatments for CH.

---

**Anticonvulsants in Migraine Prophylaxis**

Cochrane DB Syst Rev 2009;3:CDO00226

**Study**

Meta-analysis of prospective, controlled trials of anticonvulsant drugs in migraine headache prophylaxis.

**Results**

Twenty-three studies (n=2,927) were included. Anticonvulsants reduce migraine frequency and reasonably well-tolerated. Valproate and topiramate are the two most studied but further studies of head-to-head comparisons between agents is needed.
Migraine Headaches

Definition (Common Migraine)
- ≥5 attacks fulfilling each of the following criteria
  - 4-72 h duration
  - 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  - 1 of the following: N/V, photophobia/phonophobia/osmophobia

Epidemiology
- 18% females, 6% males; frequency decreases with age (especially at menopause)

Etiology and Pathophysiology
- theories of migraine etiology
  - depolarizing wave of “cortical spreading depression” across the cerebral cortex that may cause an aura (e.g. visual symptoms due to wave through occipital cortex) and also activate trigeminal nerve afferent fibers
  - possible association with vasoconstriction/dilation
- significant genetic contribution
- triggers: stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrites (e.g. processed meats)

Signs and Symptoms
- stages of uncomplicated migraine
  1. prodrome (hours to days before headache onset)
  2. aura
  3. headache (see Table 24 for description of typical headache)
  4. postdrome
- aura
  - fully reversible symptom of focal cerebral dysfunction lasting <60 min
  - examples: visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots), unilateral paresthesia and numbness or weakness, aphasia
- prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
- classification of migraines
  - common migraine: no aura
  - classic migraine: with aura (headache follows reversible aura within 60 min)
  - complicated migraine: with severe/persistent sensorimotor deficits
  - examples
    - basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness)
    - hemiplegic/hemisensory migraine
    - ophthalmoplegic migraine
  - acephalgic migraine (i.e. migraine equivalent): aura without headache

Management
- avoid triggers
- mild to moderate migraine
  - 1st line: NSAIDs (ibuprofen, naproxen)
  - moderate to severe migraine
    - triptans (most effective), ergots (dihydroergotamine, DHE)
    - migraine prophylaxis: anticonvulsants (divalproex, topiramate, gabapentin), TCA (amitryptiline, nortriptyline), propranolol, calcium channel blocker (verapamil)

Sleep Disorders

Overview of Sleep

Definition
- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many elderly have reduced sleep as a consequence of underlying sleep disorders

Sleep Architecture
- polysomnogram (PSG) measures: EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG
Table 27. Sleep Stage Characteristics

<table>
<thead>
<tr>
<th>Stage</th>
<th>EEG</th>
<th>EOG</th>
<th>Muscle Tone</th>
<th>Other Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waking State</td>
<td>Low voltage high frequency, dominant α rhythm (8-13 Hz)</td>
<td>Rapid, blinking</td>
<td>High</td>
<td>Marker for very light quality sleep or sleep disruption</td>
</tr>
<tr>
<td>Stage N1 (~5%)</td>
<td>&lt;50% α activity replaced with θ (4-7 Hz), vertex waves</td>
<td>Slow, roving eye movements</td>
<td>High, but gradually dropping</td>
<td></td>
</tr>
<tr>
<td>Stage N2 (~50%)</td>
<td>K complexes high voltage negative and positive discharges with spindles (11-16 Hz)</td>
<td>Still</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Stage N3 (previously 3 and 4)/Slow Wave/Delta Sleep (~20%)</td>
<td>Slow wave activity – high voltage (&gt; 75 µV), low frequency (&lt; 2 Hz)</td>
<td>Still</td>
<td>Low</td>
<td>Homeostatic sleep Reduced BP, HR, cardiac output, RR Growth hormone release</td>
</tr>
<tr>
<td>Rapid Eye Movement (REM) Sleep (~25%)</td>
<td>Mixed frequency, low voltage, sawtooth waves</td>
<td>Rapid eye movements</td>
<td>Very low</td>
<td>Irregular respiration Arrhythmias, heart rate variation Classical dreaming state</td>
</tr>
</tbody>
</table>

Disturbances of Alertness and Sleep

Coma
- see Neurosurgery, NS34

Insomnia
- definition/criteria
  - difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep
- types
  - sleep state misperception, psychophysiological insomnia (learned sleep-preventing associations – i.e. clock watching), fatal familial insomnia (rare prion protein mutation causing autonomic dysfunction), idiopathic (lifelong difficulty)
- secondary causes
  - psychiatric disorders (80% of psychiatric patients): anxiety and depression (see Psychiatry, PS10, PS7)
  - neurologic disorders: neurodegenerative disease, epilepsy, neuromuscular disorders, many others
  - sleep disorders: restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
  - medical conditions: pregnancy, cardiorespiratory (COPD/HF), GERD, pain (arthritis, fibromyalgia, cancer)
  - drugs/toxins: caffeine, alcohol, stimulants, antidepressants, glucocorticoids, sedative withdrawal
- treatment
  - sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, CBT

Sleep Apnea
- definition
  - disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence (or drowsiness)
- epidemiology
  - >2-4% of the population
  - increasing obesity
  - significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)
- types
  - obstructive sleep apnea: see Respiratology, R31
  - central sleep apnea: no effort to breath over 10 s
  - mixed apnea: starts as central, but eventually becomes obstructive
- etiology of central apnea: heart failure, opiates, brainstem pathology, myotonic dystrophy
- diagnosis: apnea hypopnea index (AHI) or respiratory disturbance index (RDI) should be <5 in the normal state
- treatment: conservative measures, dental devices, CPAP (common), surgery (rare), ensure driving safety

Drug Effects on Wakefulness and Sleep
- Antihistamines associated with increased sleepiness
- Stimulants increase arousal
- Caffeine (an adenosine antagonist) increases wakefulness
- Benzodiazepines reduce slow wave sleep
- Antidepressants (TCA/MAOI/SSRI) reduce REM, prolong REM latency
- Alcohol may hasten sleep onset but associated with increased arousals

Avoid sleep medications (especially in elderly patients) due to increased risk of falls, pseudodepression, and memory loss
Restless Leg Syndrome and Periodic Limb Movement in Sleep
• definition
  ▪ urge to move with accompanied uncomfortable sensations that begin or worsen with rest, are partially or totally relieved with movement, and are worse in evening/night
  ▪ RLS refers to sensation
  ▪ PLMS refers to the manifestation
• epidemiology: 10% North Americans, 90% of RLS have PLMS, 50% of patients with PLMS have RLS
• etiology: central (spasticity), peripheral nervous system (radiculopathy, neuropathy), pregnancy, iron deficiency, alcohol use
• treatment
  ▪ underlying contributors (iron and B12 supplementation), dopaminergic agonists (first line), clonazepam (causes tachyphylaxis), opioids (only exceptional circumstances)
  ▪ NOT recommended: Sinemet®, causes augmentation

Narcolepsy
• definition/clinical features: excessive daytime sleepiness (all narcolepsy), cataplexy = loss of muscle tone with emotional stimuli (pathognomonic), sleep paralysis (unable to move upon wakening), hypnogogic hallucinations (vivid dreams or hallucinations at sleep onset)
• epidemiology: prevalence 1:2,000, onset in adolescence/early adulthood; life-long disorder
• etiology: presumed autoimmune attack on orexin/hypocretin system, post head injury, MS, hypothalamic tumors; rarely familial
• diagnosis: based on clinical history + multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps
• treatment
  ▪ sleep hygiene and scheduled brief naps, restricted driving
  ▪ alerting agents modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
  ▪ anti-cataplectic: TCAs, SSRIs, sodium oxybate

Parasomnias
• definition/clinical features: unusual behaviors in sleep with clinical features appropriate to stage of sleep
• etiology: in elderly, REM sleep behavior disorder may be associated with PD; in children, slow wave sleep arousals (sleep walking) may be associated with sleep disordered breathing
• diagnosis: clinical history in children, polysomnography in adults to exclude nocturnal seizures
• treatment: behavioral management (safety, adequate sleep); clonazepam for REM sleep behavior, tonsillectomy if appropriate in children

Circadian Rhythm
• definition/clinical features: abnormalities based on time of day rather than sleep (i.e. jet lag, shift work)
• diagnosis: clinical history

CNS Infections
• see Infectious Diseases, ID19

Spinal Cord Syndromes
• see Neurosurgery, NS27

Stroke

Terminology
• stroke: sudden onset of neurological deficits of a vascular basis with infarction of CNS tissue
  ▪ infarction is permanent tissue injury (confirmed by neuroimaging)
• TIA: sudden onset of neurological deficits of a vascular basis without infarction (i.e. resolution)
Pathophysiology

- two major types: ischemic (~80%) and hemorrhagic (~20%)

1. Ischemic
   - **arterial thrombosis**: thrombus formation in artery (local/in situ)
     - large vessel: stenosis or occlusion of the internal carotid artery, vertebral, or intracranial arteries
       - mechanisms
         - insufficient blood flow beyond lesion (hemodynamic stroke)
         - underlying processes: atherosclerosis (most common cause), dissection, and vasculitis
   - small vessel/lacunar
     - mechanism: chronic HTN and DM cause vessel wall thickening and decreased luminal diameter
     - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule, and thalamus)
   - cardioembolic: blockage of cerebral arterial blood flow due to particles originating from a cardiac source
     - atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
   - systemic hypoperfusion (global cerebral ischemia)
     - inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest, arrythmia, or MI)
     - primarily affects watershed areas (between the major cerebral arterial territories)

2. Hemorrhagic
   - intracerebral hemorrhage
     - mechanisms
       - hypertensive (most common): rupture of small microaneurysms (Charcot-Bouchard aneurysms) causing intraparenchymal hemorrhage
       - most common sites: putamen, thalamus, cerebellum, and pons
       - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, vasculitis, drug use (cocaine or amphetamines)
   - subarachnoid hemorrhage see Neurosurgery, NS18

Stroke Syndromes According to Vascular Territory

- **ACA**: contralateral leg paresis and sensory loss
- **MCA**: proximal occlusion involves
  1. contralateral weakness and sensory loss of face and arm
  2. cortical sensory loss
  3. may have contralateral homonymous hemianopia or quadrantanopia
  4. if left hemisphere: aphasia
  5. if right hemisphere: neglect
  6. eye deviation towards the side of the lesion and away from the weak side
- **PCA**
  1. contralateral hemianopia or quadrantanopia
  2. midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  3. thalamic findings: sensory loss, amnesia, decreased level of consciousness
  4. if bilateral: cortical blindness or prosopagnosia
- **basilar artery** (locked-in syndrome)
  1. quadriparesis
  2. dysarthria
  3. impaired eye movements
- **PICA** (lateral medullary or Wallenberg syndrome): ipsilateral ataxia, ipsilateral Horner’s, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, N/V, dysphagia, dysarthria, hiccups
- **medial medullary infarct** (anterior spinal artery, which can be associated with anterior cord infarct): contralateral hemiparesis (focal sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness
- **lacunar infarcts** (deep hemispheric white matter)
  - pure motor hemiparesis (posterior limb of internal capsule): contralateral arm, leg, and face
  - pure sensory loss (thalamic): hemisensory loss
  - ataxic hemiparesis: ipsilateral ataxia and leg paresis
  - dysarthria-clumsy hand syndrome: dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness

HTN Encephalopathy

Acute severe HTN (typically dBP >130 or sBP >200) can cause hypertensive encephalopathy – abnormal fundoscopic exam (papilledema, hemorrhages, exudates, cotton-wool spots), focal neurologic symptoms, N/V, visual disturbances and change in LOC

Consider transfer of acute stroke patient to a designated stroke center for neuroprotective or thrombolytic therapy if the patient is seen in first few hours

Early seizure activity occurs in 5-25% of patients after ICH

Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can also have seizures, focal neurological deficits, or cranial nerve palsies. This is diagnosed with MRV or CTV. Treatment is typically anticoagulation with heparin initially, then transition to warfarin

20-40% of patients with ischemic stroke may develop hemorrhagic transformation within 1 wk after the initial infarction
Assessment and Treatment of Ischemic Stroke

General Assessment
- ABCs, full vital sign monitoring, check glucose, urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis)
- history
  - onset: time when last known to be awake and symptom free
  - mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
- investigations
  - non-contrast CT head (STAT): to rule out hemorrhage and assess extent of infarct
  - ECG: to rule out atrial fibrillation (cardioembolic cause)
  - CBC, electrolytes, creatinine, PTT/INR, blood glucose
- imaging (i.e. CT) signs of stroke
  - loss of cortical white-gray differentiation
  - sulcal effacement (i.e. mass effect decreases visualization of sulci)
  - hypodensity of parenchyma
  - insular ribbon sign
  - hyperdense MCA sign

ACUTE STROKE MANAGEMENT

1. Thrombolysis
   - rtPA (recombinant tissue plasminogen activator)
   - given within 4.5 h of acute ischemic stroke onset provided there are clinical indications and no contraindications to use
   - indications: based on NIH Stroke Scale
   - contraindications: see sidebar

2. Anti-Platelet Therapy
   - give at presentation of TIA or stroke if rtPA not received
   - antiplatelet agents
     - ASA: recommended dose 81 mg chewed
     - if patient intolerant to ASA, use other antiplatelet agent (i.e. clopidogrel)

Aspect Score: 10-point quantitative score to assess ischemic changes on CT scan
- 10/10 is normal and <4/10 signifies high risk of bleed with rtPA
- Subtract 1 point for each of following structures if abnormal within the ischemic hemisphere: caudate, lentiform, insula, internal capsule, MCA 1, 2, 3, 4, 5, 6 regions

Infarcted area of brain tissue can often appear normal on CT during the first several hours after the onset of stroke

Blood work should only delay treatment if: patient is on anticoagulants, low platelet count suspected, abnormal electrolytes suspected, or any bleeding abnormality suspected

Suspect an alternate diagnosis if: fever, decreased LOC, fluctuating symptoms, gradual onset, no focal neurological symptoms, and/or positive symptoms

If rtPA given at stroke onset, delay acute antiplatelet/anticoagulation treatment by 24 h

Blood work should only delay treatment if: patient is on anticoagulants, low platelet count suspected, abnormal electrolytes suspected, or any bleeding abnormality suspected

The National Institute of Health Stroke Scale (NIHSS) is a standardized clinical examination that determines the severity of an acute stroke; it can also be used to monitor response to treatment over time
The scale uses 11 items that evaluate:
- Level of consciousness
- Visual system
- Motor system
- Sensory system
- Language abilities
Scoring (x/42):
0=no stroke
1-4=mild stroke
5-15=moderate stroke
15-20=moderate to severe stroke
21-42=severe stroke
rtPA should be considered if score 6 or greater

Absolute Contraindications to rtPA
Hx: improving sx, minor sx, seizure at stroke onset, recent major surgery (within 14 d) or trauma, recent GI or urinary hemorrhage (within 21 d), recent LP or arterial puncture at noncompressible site, PMHx ICH, sx of SAH/pericardia/MI, pregnancy
P/E: sBP ≥185, dBP ≥110, aggressive treatment to decrease BP uncontrolled serum glucose, thrombocytopenia
Ix: hemorrhage or mass on CT, high INR or aPTT
3. Acute Anti-Coagulant Therapy
- for patients with TIA or stroke and atrial fibrillation if rtPA not received
  - recommend IV heparin (or ensuring INR between 2-3 if already anticoagulated on warfarin)

Other Acute Management Issues
- avoid hyperglycemia which can increase the infarct size
- lower temperature if febrile
- prevent complications
  - NPO if dysphagia (to be reassessed by SLP)
  - DVT prophylaxis if bed-bound
  - initiate rehabilitation early

Blood Pressure Control
- do NOT lower the blood pressure unless the HTN is severe
  - antihypertensive therapy is withheld for at least 5 d after thromboembolic stroke unless sBP >220 mmHg or dBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection
- acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
- most patients with an acute cerebral infarct are initially hypertensive and their BP will fall spontaneously within 1-2 d
- IV labetalol first-line if needed

Etiological Diagnosis
- further investigations
  - additional neuroimaging (MRI)
  - vascular imaging: CTA/MRA/carotid dopplers
  - cardiac tests: ECHO, holter monitoring
- correct etiological diagnosis is critical for appropriate secondary prevention strategies

Primary and Secondary Prevention of Ischemic Stroke

Anti-Platelet Therapy
- primary prevention
  - current evidence has not firmly established a protective role for antiplatelet agents for low-risk patients without a prior stroke/TIA
- secondary prevention
  - ASA is the initial antiplatelet of choice for stroke prevention
  - other agents (generally reserved for those who suffer cerebrovascular symptoms while on ASA or if unable to tolerate ASA)
    - Aggrenox® (ESPRIT trial)
    - clopidogrel (CAPRIE trial)

Carotid Stenosis
- primary prevention (asymptomatic)
  - carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per y; carotid endarterectomy reduces the risk of stroke by 1% per y (but 5% risk of complications)
- secondary prevention (previous stroke/TIA in carotid territory)
  - carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%), and is less beneficial for those with symptomatic moderate stenosis (50-69%) (NASCET trial), see Vascular Surgery, VS10
- according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI, and death; however, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI

Atrial Fibrillation
- primary and secondary prevention with anticoagulation
  - risk stratification using CHADS² score
    - 0 (very low risk): antiplatelet
    - 1 (low risk): anticoagulant or antiplatelet – patient specific decision
    - >2 (mod-high risk): anticoagulant
- anticoagulation therapy
  - warfarin (titrate to INR 2-3)
  - dabigatran (110 or 150 mg bid) may be an option to warfarin, but should be used cautiously due to lack of a reversal agent should bleeding occur
### Hypertension
- **Primary prevention**
  - Targets: BP <140/90 (or <130/80 for diabetics or renal disease)
  - Ramipril 10 mg PO OD is effective in patients at high risk for cardiovascular disease (HOPE trial)
  - ACEI reduce the risk of stroke beyond their antihypertensive effect

- **Secondary prevention**
  - ACEI and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

### Hypercholesterolemia
- **Primary prevention**
  - Statins reduce the risk of stroke in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE trial)

- **Secondary prevention**
  - Statins reduce risk of subsequent stroke – best evidence is for high dose atorvastatin (SPARCL trial) but lower doses may be more appropriate if patient cannot tolerate high dose

### Diabetes
- Ideal management: HbA1c <7%, fasting blood glucose between 4 and 7

### Smoking
- **Primary prevention**
  - Smoking increases risk of stroke in a dose-dependent manner

- **Secondary prevention**
  - After smoking cessation, the risk of stroke decreases to baseline within 2-5 yr

### Physical Activity
- Regular physical activity is an important lifestyle measure in stroke prevention and its beneficial effect has a dose-related response in terms of intensity and duration of activity

### Stroke Rehabilitation
- Individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services

- Multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

### Cerebral Hemorrhage

#### Investigations
- General investigations, see *Assessment and Treatment of Ischemic Stroke*, N49
- Further investigations
  - LP (if suspect subarachnoid hemorrhage despite negative CT)
  - May require cerebral angiogram if suspect aneurysm or AVM
  - If typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion

#### Management
- **Medical**
  - Anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2010 AHA/ASA guidelines suggest that reducing sBP to as low as 140 mmHg with IV anti-hypertensives is safe and appropriate management (target sBP 140-160)
  - ICP lowering medical management (if necessary): see *Neurosurgery*, NS7

- **Surgical:** see *Neurosurgery*, NS19
Multiple Sclerosis

Definition
- a chronic inflammatory disease of the CNS characterized by relapsing remitting, or progressive neurologic symptoms due to inflammation, demyelination, and axonal degeneration

Clinical Patterns of MS
- relapsing remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing (PRMS) 5%, secondary progressive (SPMS)
- most RRMS goes on to become SPMS

MS Variants
- Devic’s = neuromylitis optica (NMO): severe optic neuritis and extensive transverse myelitis extending >3 vertebral segments (NMO antibody positive)
- clinically isolated syndrome (CIS): single MS-like episode, which may progress to MS
- tumefactive MS: solitary lesion >2 cm mimicking neoplasms on MRI
- fulminant MS (Marburg): rapidly progressive and fatal MS associated with severe axonal damage, inflammation, and necrosis
- acute disseminated encephalomyelitis (ADEM): monophasic demyelinating disorder with multifocal neurologic symptoms seen mainly in children often following infection or vaccination

Etiology
- genetic
  - polygenic: the HLA-DRB1 gene has been demonstrated to be a genetically susceptible area
  - 30% concordance for monzygotic twins, 2-4% risk in offspring of affected mother or father
- environmental
  - MS is more common in regions with less sun exposure and lower stores of vitamin D (Europe, Canada, US, New Zealand, SE Australia)
  - MS has also been linked to certain viruses (EBV is associated with MS)

Epidemiology
- onset 17-35 yr; F:M = 3:1
- PPMS occurs in an older population with F=M

Diagnosis
- dissemination in space and in time as based on the revised McDonald criteria
  - dissemination in time: 2 or more attacks, new gadolinium enhancing lesion 3 mo later, or new T2 lesions >1 mo after first attack
  - dissemination in space: clinical evidence of 2 or more lesions; or three of (1 gadolinium enhancing or 9 T2 lesions), (1 infratentorial lesion), (1 juxtacortical lesion), (3 periventricular lesions)

Clinical Features
- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. INO), impaired gait, vertigo, bladder dysfunction
- Lhermitte’s sign: flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- Uhthoff’s phenomenon: worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically weakness of legs in pyramidal distribution paired with cerebellar findings of arms (i.e. intention tremor)
- symptoms not commonly found in MS: visual field defects, aphasia, apraxia, progressive hemiparesis
- relapse: acute/subacute onset of clinical dysfunction that peaks from days to weeks, followed by remission with variable symptom resolution (symptoms must last at least 24 h)
- in RRMS, average 0.4 to 0.6 relapses/yr, but higher disease activity in first yr of disease

Investigations
- MRI: demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
  - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxta cortical region, and dorsolateral spinal cord
- Dawson’s fingers: periventricular lesions extending into corpus callosum
- cranial MRI is more sensitive than spinal MRI
- CSF: oligoclonal bands in 90%, increased IgG concentration
- evoked potentials (visual/auditory/somatosensory): delayed but well-preserved wave forms

Clinical Outcomes
- Disability progression and is scored from 0 to 10 based on the neurologic exam and ambulation
- The Expanded Disability Status Scale (EDSS) is used as a measure of disability progression and is scored from 0 to 10 based on the neurologic exam and ambulation

Conclusions
- IFN-β treatment can delay progression to clinically definite MS in patients with CIS over 2 yr.
Treatment

- **acute treatment**: methylprednisolone 1,000 mg IV daily x 3-7 d (no taper required); if poor response to corticosteroids may consider plasma exchange

- **disease modifying therapy**
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: interferon-β (injection: Betaseron®, Avonex®, Rebif®), glatiramer acetate (injection: Copaxone®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion)
  - new oral agents: fingolimod (available) and cladribine (not yet available)
    - indications for fingolimod: newly diagnosed patients with active RRMS who prefer oral treatment despite increased risks or those intolerant of first line therapies
  - CIS: early treatment with interferons may delay potential second attack
  - RRMS: DMT reduces rate of relapse by about 30%
  - PPMS/SPMS: no proven efficacy of DMTs

- **symptomatic treatment**
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantidine, modafinil, methylphenidate
  - depression: antidepressant, lithium
  - constipation: high fiber intake, stool softener, laxatives
  - sexual dysfunction: sildenafil, tadenafil, vardenafil

- **education and counseling**: MS Society, support groups, psychosocial issues

Prognosis

- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy

---

**Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis**

**NEJM** 2010;362:402-415

**Method:** Multicenter double-blind RCT.

**Population:** 1,292 patients with relapsing-remitting MS and at least one relapse.

**Intervention:** Oral fingolimod at 0.5-1.25 mg or 30 µg IM interferon-β.

**Outcomes:** Annualized relapse rate over 1 yr; lesions on T2-weighted MRI.

**Results:** Annualized relapse rate was lower in both groups receiving fingolimod compared to interferon: 0.20 (95% CI 0.16-0.26) with 1.25 mg fingolimod, 0.16 (95% CI 0.12-0.21) with 0.5 mg fingolimod, 0.33 with interferon (95% CI 0.26-0.42; p<0.001). MRI findings also showed greater reduction of lesions in fingolimod-treated patients. Progression of disability was unchanged. Side effects included severe infections like HSV encephalitis, disseminated VZV, other HSV infections, and skin cancer.

**Conclusions:** Oral fingolimod is superior to interferon-β injections in reducing relapses and MRI lesion load in patients with MS.
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<th>Indications</th>
<th>Mechanism of Action/Class</th>
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<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Side Effects</th>
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<tr>
<td>Parkinson’s Disease</td>
<td>Dopamine precursor</td>
<td>levodopa</td>
<td>Sinemet®</td>
<td>Carbidopa 25 mg/levodopa 100 mg PO tid Maximum 200 mg carbidopa and 2,000 mg levodopa per day</td>
<td>Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions</td>
<td>Nausea, hypotension, hallucinations, dyskiniesias in last 14 d, history of melanoma or undiagnosed skin lesions</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>bromocriptine</td>
<td>Parlodel®</td>
<td>1.25 mg PO bid, increase by 2.5 mg/d q2-4wk, up to 10-30 mg PO tid</td>
<td>Concomitant use of potent inhibitors of CYP3A4, uncontrolled HTN, ischemic heart disease, peripheral vascular disease; caution with renal or hepatic disease</td>
<td>Hypotension, N/V, diziness, constipation, diarrhea, abdominal cramps, H/A, nasal congestion, drowsiness, hallucinations</td>
</tr>
<tr>
<td>MAO B inhibitor</td>
<td>selegiline</td>
<td>Edempyl®</td>
<td></td>
<td>5 mg PO bid</td>
<td>Concomitant use of meperidine or tricyclic antidepressants</td>
<td>H/A, insomnia, diziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinsia, risk of hypertensive crisis with tyramine-containing foods</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Acetylcholinesterase</td>
<td>pyridostigmine</td>
<td>Mestinon®</td>
<td>600 mg/d PO divided in 5-6 doses Range 60-1,500 mg/d</td>
<td>Gl or GU obstruction</td>
<td>N/V, diarrhea, abdominal cramps, increased pentaxis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness</td>
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<tr>
<td>Acute Migraine</td>
<td>Triptan (selective 5-HT1D receptor agonist)</td>
<td>sumatriptan</td>
<td>Imitrex®</td>
<td>25-100 mg PO pm, maximum 200 mg/d</td>
<td>Hemiplegic/basilar migraine, ischemic heart disease, cerebrovascular disease, uncontrolled HTN, use of ergotamine-5-HT1 agonist in past 24 h, use of MAO inhibitor in last 14 d, severe hepatic disease</td>
<td>Vertigo, chest pain, flushing, sensation of heat, hypertensive crisis, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, N/V, H/A, hyposalivation, fatigue</td>
</tr>
<tr>
<td></td>
<td>Ergot (5-HT1D receptor agonist)</td>
<td>dihydroergotamine</td>
<td>Migranal®</td>
<td>Nasal spray 0.5 mg/spray, maximum 4 sprays/d</td>
<td>Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled HTN, ischemic heart disease, peripheral vascular disease, use of triptans in last 24 h, use of MAO inhibitors in last 14 d</td>
<td>Coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation; may cause significant rebound H/A</td>
</tr>
<tr>
<td>Migraine Prophylaxis</td>
<td>Anticonvulsant</td>
<td>topiramate</td>
<td>Topamax®</td>
<td>25 mg OD PO (in evening); may increase weekly by 25 mg/d to a max 50 mg bid</td>
<td>Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma</td>
<td>Sedation, mood disturbance, cognitive dysfunction, anorexia, nausea, diarrhea, paresthesias, metabolic acidosis, glaucoma, SJS/TEN</td>
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<tr>
<td></td>
<td>(β-blocker)</td>
<td>propranolol</td>
<td>Inderal®</td>
<td>80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q6-8h</td>
<td></td>
<td>Fatigue, cognitive dysfunction, disturbed sleep, rashes, dyspepsia, dry eyes, heart failure, bronchospasm, risk of acute tachycardia and HTN if withdrawal</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Anticonvulsant for partial ± 2º generalization, generalized tonic-clonic</td>
<td>carbamazepine</td>
<td>Tegretol® (Carbatrol)</td>
<td>Start at 100-200 mg PO OD-tid increase by 200 mg/d up to 800-1,200 mg/d</td>
<td>History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d</td>
<td>Drowsiness, H/A, unsteadiness, diziness, N/V, skin rash, agranulocytosis/aplastic anemia (rare)</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant for partial, tonic-clonic, status epilepticus</td>
<td>phenytoin</td>
<td>Dilantin®</td>
<td>100 mg PO tid, maintenance dose up to 200 mg PO tid SE: 10-15 mg/kg IV loading dose then maintenance doses of 100 mg PO or IV q6-8h</td>
<td>Hypersensitivity, pregnancy, breastfeeding; caution with F-450 interactions</td>
<td>Hypotension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, H/A, blood dyscrasias, nystagmus, N/V, constipation, sedation, teratogenic</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant for partial or generalized, absence seizures</td>
<td>valproic acid</td>
<td>Depacon® Depakene® Depakote®</td>
<td>10-15 mg/kg/d PO in divided doses, increase incrementally until therapeutic dose to max of 60 mg/kg/d</td>
<td>Hypersensitivity, hepatic disease, urea cycle disorders</td>
<td>Hepatic failure, H/A, somnolence, alopecia, N/V, diarrhea, tremor, diplopia, thrombocytopenia, hypothermia, pancreatitis, encephalopathy</td>
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<tr>
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<td>Anticonvulsant for absence seizures</td>
<td>ethosuximide</td>
<td>Zarontin®</td>
<td>500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses</td>
<td>Hypersensitivity (succinimides)</td>
<td>CNS depression, blood dyscrasias, SLE, SJS, GI symptoms</td>
</tr>
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</table>
Table 28. Common Medications – Major Issues (continued)

<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action/Class</th>
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<tr>
<td>Stroke Prevention in AF</td>
<td>Anticoagulant (direct thrombin inhibitor)</td>
<td>dabigatran</td>
<td>Pradax®</td>
<td>110 mg PO bid or 150 mg PO bid</td>
<td>CrCl &lt; 30 mL/min, significant hemostatic impairment or CNS lesions within 6 mo with high risk of bleeding</td>
<td>Dyspepsia, gastritis, bleeding</td>
</tr>
<tr>
<td>Mild to Moderate AD or DLB</td>
<td>Cholinesterase Inhibitor</td>
<td>donepezil</td>
<td>Aricept®</td>
<td>5 mg PO OD, may increase to 10 mg PO OD after 4-6 wk</td>
<td>Hypersensitivity to donepezil or to piperidine derivatives</td>
<td>Diarrhea, N/V, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>MS Disease Modifying Therapy</td>
<td>interferon-β-1b</td>
<td>Betaseron®</td>
<td>0.25 mg (8 MU) SC every other day</td>
<td>Pregnancy, hypersensitivity to natural or recombinant interferon-β</td>
<td>Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time)</td>
</tr>
<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>interferon-β-1a SC</td>
<td>Rebif®</td>
<td>44 μg SC 3 times/wk</td>
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<td></td>
<td>MS Disease Modifying Therapy</td>
<td>interferon-β-1a IM</td>
<td>Avonex®</td>
<td>30 μg IM once weekly</td>
<td></td>
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<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>glatiramer acetate</td>
<td>Copaxone®</td>
<td>20 mg SC OD</td>
<td>Hypersensitivity to glatiramer or mannitol</td>
<td>Injection site reactions, nausea, transient chest pain, vasodilation</td>
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<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>natalizumab</td>
<td>Tysabri®</td>
<td>300 mg IV given over 1 h, every 4 wk</td>
<td>Hypersensitivity to natalizumab, progressive multifocal leukoencephalopathy (PML)</td>
<td>Rash, nausea, arthralgia, H/A, infections, rare risk of PML and melanoma</td>
</tr>
<tr>
<td></td>
<td>MS Disease Modifying Therapy</td>
<td>fingolimod</td>
<td>Gilenya®</td>
<td>0.5 mg PO OD</td>
<td>Not available</td>
<td>Diarrhea, transaminisits, H/A, bradyarrhythmia, lymphocytopenia</td>
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<tr>
<td>Spasticity (i.e. MS)</td>
<td>Muscle Relaxant – Antispastic</td>
<td>baclofen</td>
<td>Lioresal® (injectable)</td>
<td>5 mg PO tid, increase by 15 mg/d q3d to max dose 80 mg/d in three divided doses</td>
<td>Hypersensitivity to baclofen</td>
<td>Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea</td>
</tr>
</tbody>
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Landmark Neurology Trials

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<th>Reference</th>
<th>Results</th>
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<tr>
<td>CREST</td>
<td>NEJM 2010;363:11-23</td>
<td>Carotid stenting and endarterectomy had similar benefits in reduction of stroke, MI, and death in carotid stenosis, but in the periprocedural period, stenting had a higher rate of stroke, while endarterectomy had a higher rate of MI</td>
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<tr>
<td>ECASS 3</td>
<td>NEJM 2008;359:1317-29</td>
<td>rtPA improved clinical outcomes when administered within 3 to 4.5 h of acute ischemic stroke</td>
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<tr>
<td>Interferon-β Multiple Sclerosis Study Group Trial</td>
<td>Neurology 1993;43:655-61</td>
<td>Interferon-β-1b reduces relapse rate and severity of relapses in RRMS</td>
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<tr>
<td>NASCET</td>
<td>NEJM 1991;7:445-53</td>
<td>Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy</td>
</tr>
<tr>
<td>NINDS rtPA</td>
<td>NEJM 1995;333:1581-7</td>
<td>rtPA reduces mortality and long-term disability when administered within 3 h of acute stroke</td>
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<td>PROGRESS</td>
<td>NEJM 2008;359:1238-51</td>
<td>ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention</td>
</tr>
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<td>RELY</td>
<td>NEJM 2009;361:1139</td>
<td>Darbepetran superior to warfarin for stroke prevention in patients with atrial fibrillation</td>
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<tr>
<td>SPARCL</td>
<td>NEJM 2006;355:549-59</td>
<td>The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA</td>
</tr>
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</table>

References

Corna

Common Presenting Complaints

Disorders of Consciousness

Drug Information

Epilepsy
Lowenstein DH, Aldridge BK. Status epilepticus. NEJM 1998;339:970-976.

General

Headache
Dorsey ME, McDonald DR, Baerlocher MO, et al. Does this patient have headache or need neuroimaging? JAMA 2006;296:1274-1283.

Movement Disorders

Multiple Sclerosis
# Neurosurgery

Francois Mathieu, David Ben-Israel, and Mostafa Fatehi Hassanabad, chapter editors
Khaled Ramadan, Karim Virani, and Vahagn Karapetyan, associate editors
Alexa Bramall, EBM editor
Dr. Todd Mainprize and Dr. Eric Massicotte, staff editors

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**Acronyms**

AVF arteriovenous fistula  
AVM arteriovenous malformation  
CSF cerebral spinal fluid  
CPA cerebellar pontine angle  
CPP cerebral perfusion pressure  
CVR cerebral vascular resistance  
DBS deep brain stimulation  
DI diabetes insipidus  
ECF extracellular fluid  
EMG electromyography  
EVD external ventricular drain  
GCS Glasgow coma scale  
GPI globus pallidus pars interna  
H/A headache  
IC internal capsule  
ICH intracerebral hemorrhage  
ICP intracerebral pressure  
IVH intraventricular hemorrhage  
LMN lower motor neuron  
LOC loss of consciousness  
LP lumbar puncture  
MAP mean arterial pressure  
MCS microsurgical clipping  
MRS magnetic resonance spectroscopy  
MRS magnetic resonance imaging  
PAG periaqueuctal gray matter  
PET positron emission tomography  
PLL posterior longitudinal ligament  
PHET primitive neuroectodermal tumor  
PVG periventricular gray matter  
SAH subarachnoid hemorrhage  
SDH subdural hemorrhage  
SIADH syndrome of inappropriate antidiuretic hormone  
SPECT single photon emission computed tomography  
SRS stereotactic radiosurgery  
STN subthalamic nucleus  
UMN upper motor neuron  
VPL ventral posterolateral  
VPM ventral posteromedial  
WBRT whole brain radiation therapy

**Basic Anatomy Review**

**MRI Brain**

A. Sagittal Section  
B. Axial Section

**Figure 1.** Magnetic resonance imaging (MRI) neuroanatomy  

**Figure 2.** Relationship of nerve roots to vertebral level in the cervical and lumbar spine  
Note: AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement

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Figure 3. Vascular supply of the brain. Please refer to legend for artery names. 3A. Circle of Willis, most common variant. 3B. Vascular territories of the brain and brainstem, sagittal view, seen laterally. 3C. Vascular territories of the brain and brainstem, sagittal view, seen medially.

Differential Diagnoses of Common Neurosurgical Presentations

<table>
<thead>
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<th>Intracranial Mass Lesions</th>
<th>Disorders of the Spine</th>
<th>Peripheral Nerve Lesions</th>
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<tr>
<td>Tumor</td>
<td>Extravascular</td>
<td>Neuropathies</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Degenerative: disc herniation, canal stenosis, spondylothesis/spondylosis</td>
<td>Traumatic</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Infection/inflammation: osteomyelitis, discitis</td>
<td>Entrapments</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Ligamentous: ossification of posterior longitudinal ligament (OPLL)</td>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Vestibular schwannoma (acoustic neuroma)</td>
<td>Trauma: mechanical compression/instability, hematoma</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>Tumors (55% of all spinal tumors): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma</td>
<td>Tumors (40% of all spinal tumors): meningioma, schwannoma, neurofibroma</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>Intradural extramedullary</td>
<td>Vascular: dural arteriovenous fistula, subdural hematoma (especially if on anticoagulants)</td>
</tr>
<tr>
<td>Pus/inflammation</td>
<td>Tumors (40% of all spinal tumors): meningioma, schwannoma, neurofibroma</td>
<td>Tumors (5% of all spinal tumors): astrocytomas and ependymomas most common; also hemangioblastomas and dermoids</td>
</tr>
<tr>
<td>Cerebral abscess, extradural abscess, subdural empyema</td>
<td>Intradural intramedullary</td>
<td>Syringomyelia (common causes: trauma, congenital, idiopathic)</td>
</tr>
<tr>
<td>Encephalitis (see Infectious Diseases, ID20)</td>
<td>Tumors (40% of all spinal tumors): meningioma, schwannoma, neurofibroma</td>
<td>Infectious/inflammatory: TB, sarcoi, transverse myelitis</td>
</tr>
<tr>
<td>Tumefactive MS</td>
<td></td>
<td>Vascular: AVM, ischemia</td>
</tr>
</tbody>
</table>

Blood

Extradural

Degenerative: disc herniation, canal stenosis, spondylothesis/spondylosis
Infection/inflammation: osteomyelitis, discitis
Ligamentous: ossification of posterior longitudinal ligament (OPLL)
Trauma: mechanical compression/instability, hematoma
Tumors (55% of all spinal tumors): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma
Intradural extramedullary
Vascular: dural arteriovenous fistula, subdural hematoma (especially if on anticoagulants)
Tumors (40% of all spinal tumors): meningioma, schwannoma, neurofibroma
Intradural intramedullary
Tumors (5% of all spinal tumors): astrocytomas and ependymomas most common; also hemangioblastomas and dermoids
Syringomyelia (common causes: trauma, congenital, idiopathic)
Infectious/inflammatory: TB, sarcoi, transverse myelitis
Vascular: AVM, ischemia
INTRACRANIAL PATHOLOGY

Intracranial Pressure Dynamics

Table 1. Approach to Intracranial Pathology

<table>
<thead>
<tr>
<th>Issue</th>
<th>Time Frame</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Sudden</td>
<td>No H/A = occlusive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H/A = hemorrhagic</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hours to days</td>
<td>Affects entire CNS</td>
</tr>
<tr>
<td>Infectious</td>
<td>Days to weeks</td>
<td>Often a source of infection on history</td>
</tr>
<tr>
<td>Tumor</td>
<td>Months</td>
<td>Increased ICP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initially → H/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Constant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Progressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Worse in morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As ICP increases:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blurry vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Projectile vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severely raised ICP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cushing’s reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Respiratory changes</td>
</tr>
</tbody>
</table>

Table 2. Consequences of Common Brain Lesions

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>1. Disinhibition</td>
</tr>
<tr>
<td></td>
<td>2. Concentration deficits</td>
</tr>
<tr>
<td></td>
<td>3. Orientation deficits</td>
</tr>
<tr>
<td></td>
<td>4. Judgment deficits</td>
</tr>
<tr>
<td></td>
<td>5. ± Primitive reflex re-emergence</td>
</tr>
<tr>
<td></td>
<td>6. ± Contralateral motor deficits if motor cortex involved</td>
</tr>
<tr>
<td>Frontal lobe (in inferior frontal gyrus of dominant hemisphere)</td>
<td>1. Non-fluent aphasia</td>
</tr>
<tr>
<td></td>
<td>2. Repetition impaired</td>
</tr>
<tr>
<td></td>
<td>3. Comprehension relatively spared</td>
</tr>
<tr>
<td>Broca’s area (inferior frontal gyrus of dominant hemisphere)</td>
<td>1. Fluent aphasia</td>
</tr>
<tr>
<td></td>
<td>2. Repetition impaired</td>
</tr>
<tr>
<td></td>
<td>3. Comprehension markedly impaired</td>
</tr>
<tr>
<td>Wernicke’s area (superior temporal gyrus of dominant hemisphere)</td>
<td>1. Hemispatial neglect syndrome</td>
</tr>
<tr>
<td></td>
<td>• Contralateral agnosia</td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>Contralateral visual field deficits</td>
</tr>
<tr>
<td>Right parietal lobe</td>
<td>Hemispatial neglect syndrome</td>
</tr>
<tr>
<td></td>
<td>• Contralateral agnosia</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>1. Rest tremor</td>
</tr>
<tr>
<td></td>
<td>2. Chorea</td>
</tr>
<tr>
<td></td>
<td>3. Ahetosis</td>
</tr>
<tr>
<td>Subthelial nucleus</td>
<td>Contralateral hemiballismus</td>
</tr>
<tr>
<td>Mamillary bodies (bilateral)</td>
<td>Wernicke-Korsakoff syndrome</td>
</tr>
<tr>
<td></td>
<td>1. Wernicke</td>
</tr>
<tr>
<td></td>
<td>• Confusion</td>
</tr>
<tr>
<td></td>
<td>2. Ophthalmoplegia</td>
</tr>
<tr>
<td></td>
<td>3. Ataxia</td>
</tr>
<tr>
<td></td>
<td>2. Korsakoff</td>
</tr>
<tr>
<td></td>
<td>• Anterograde amnesia</td>
</tr>
<tr>
<td></td>
<td>• Confabulation</td>
</tr>
<tr>
<td></td>
<td>• Personality changes</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Anterograde amnesia</td>
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<tr>
<td>Reticular activating system (midbrain)</td>
<td>Reduced levels of arousal and wakefulness</td>
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<tr>
<td>Paramedian pontine reticular formation</td>
<td>Gaze deviation away from side of lesion</td>
</tr>
<tr>
<td>Frontal eye fields</td>
<td>Gaze deviation toward side of lesion</td>
</tr>
<tr>
<td>Cerebellar hemisphere</td>
<td>1. Intention tremor</td>
</tr>
<tr>
<td></td>
<td>2. Limb ataxia</td>
</tr>
<tr>
<td></td>
<td>3. Fall towards side of lesion</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>1. Truncal ataxia</td>
</tr>
<tr>
<td></td>
<td>2. Dysarthria</td>
</tr>
</tbody>
</table>
ICP/Volume Relationship

- Adult skull is rigid with a constant intracranial volume
- Contents (CSF, blood, brain) are incompressible
- Increase in one constituent/space-occupying lesion = 1) increase in ICP, 2) require redistribution of CSF, blood, or brain
- However, ICP does not rise initially due to compensatory mechanisms
  - Immediate: displacement of CSF to lumbar theca, displacement of blood from venous sinuses
  - Delayed: displacement of ECF or ICF, displacement of brain tissue into compartments under less pressure (herniation)
- Once compensation is exhausted, ICP rises exponentially

Cerebral Blood Flow

- Brain receives about 15% of cardiac output (~750 mL/min)
- CBF depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR)
- Normal CPP >50 mmHg in adults
- Cerebral autoregulation maintains constant CBF by compensating for changes in CPP, unless:
  - High ICP such that CPP <60 mmHg
  - MAP >150 mmHg or MAP <50 mmHg
  - Brain injury: e.g. SAH, severe trauma

ICP Measurement

- Normal ICP <15 mmHg (8-18 cmH2O) for adult, 3-7 mmHg (4-9.5 cmH2O) for child; varies with patient position
  - Moderate elevation: increase in mean pressure >20 mmHg
  - Severe elevation: increase in mean pressure >40 mmHg
- Waveform: comprised of respiratory and cardiac pulsations (Traube-Hering waves); the amplitude increases with ICP
  - β-waves: coarse, variably increased amplitude, frequency ½-2/min, often related to respiration
  - Plateau waves: elevation of ICP over 50 mmHg lasting 5-20 min, precursor of further deterioration

Acute Monitoring

- Lumbar puncture (LP)
- Intraventricular catheter/ventriculostomy/external ventricular drain (EVD) (“gold standard”, also permits therapeutic drainage of CSF to decrease ICP)

Chronic Monitoring

- Fiber optic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

Elevated ICP

Etiology

- Intracranial space-occupying lesion
  - Tumor
  - Pus
  - Blood (trauma → hematoma [most common], subarachnoid hemorrhage)
  - Depressed skull fracture
  - Foreign body
- Increased intracranial blood volume
  - Vasodilatation (increased pCO2/decreased pO2/decreased extracellular pH, e.g. hyperventilation)
  - Venous outflow obstruction (venous sinus thrombosis, superior vena cava syndrome, space-occupying lesion)
  - Cranial dependency
- Cerebral edema
  - Vasogenic (vessel damage, e.g. hypertensive encephalopathy, tumor)
  - Cytotoxic (tissue/cell death, e.g. hypoxia, brain injury)
  - Osmotic (acute hyponatremia, hepatic encephalopathy)
• hydrocephalus
  ▪ obstructive: acquired aqueductal stenosis
  ▪ non-obstructive: decreased CSF absorption with SAH
• pseudotumor cerebri (idiopathic intracranial HTN)
• impaired autoregulation (hypotension, HTN, brain injury)
• status epilepticus (chronic seizure resulting in brain edema)

Clinical Features
1. Acute Elevated ICP
• H/A: worse in the morning, aggravated by stooping, and bending
• N/V
drop in GCS = best index to monitor progress and predict outcome of acute intracranial process (see Neurotrauma, NS29)
• papilledema ± retinal hemorrhages (may take 24-48 h to develop)
• abnormal extra-ocular movements (EOM):
  ▪ CN VI palsy: often falsely localizing (causative mass may be remote from nerve)
  ▪ upward gaze palsy (especially in children with obstructive hydrocephalus)
• herniation syndromes
• focal signs/symptoms due to lesion

2. Chronic Elevated ICP
• H/A
  ▪ postural: worsened by coughing, straining, and bending over
  ▪ morning/evening H/A → vasodilatation due to increased CO2 with recumbency
• visual changes
  ▪ due to papilledema
  ▪ enlarged blind spot, if advanced → episodic constrictions of visual fields (“gray-outs”)
  ▪ optic atrophy/blindness
  ▪ differentiate from papillitis (usually unilateral with decreased visual acuity)
• decreased level of consciousness

Investigations
• patients with suspected elevated ICP require an urgent CT/MRI
• ICP monitoring where appropriate

Herniation Syndromes

<table>
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<th>Herniation Syndrome</th>
<th>Definition</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subfalcine</td>
<td>Cingulate gyrus herniates under falx</td>
<td>Lateral supratentorial lesion</td>
<td>Usually asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Winds of impending transtentorial herniation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of ACA compression</td>
</tr>
<tr>
<td>2. Central Tentorial</td>
<td>Displacement of diencephalon through tentorial notch</td>
<td>Supratentorial midline lesion</td>
<td></td>
</tr>
<tr>
<td>(Axial)</td>
<td></td>
<td>Diffuse cerebral swelling</td>
<td>Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Late uncal herniation</td>
<td>Decreased LOC (midbrain compression), EOM/ upward gaze impairment (“sunset eyes”); compression of pretectum and superior colliculi</td>
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<td></td>
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<td></td>
<td>Brainstem hemorrhage (“Duret’s” – secondary to shearing of basilar artery perforating vessels)</td>
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<td></td>
<td>Diabetes insipidus (traction on pituitary stalk and hypothalamus), end-stage sign</td>
</tr>
<tr>
<td>3. Lateral Tentorial</td>
<td>Uncus of temporal lobe herniates down through tentorial notch</td>
<td>Lateral supratentorial lesion (often rapidly expanding traumatic hematoma)</td>
<td>Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) → ipsilateral EOM/paralysis, ptosis (CN III compression)</td>
</tr>
<tr>
<td>(Uncal)</td>
<td></td>
<td></td>
<td>Decreased LOC (midbrain compression)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Contralateral hemiplegia → extensor (upgoing) plantar response → ipsilateral hemiplegia (“Kernohan’s notch” – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle)</td>
</tr>
<tr>
<td>4. Upward</td>
<td>Cerebellar vermis herniates through tentorial incisura</td>
<td>Large posterior fossa mass (common after VP shunting)</td>
<td>Cerebellar infarct (superior cerebellar artery [SCA] compression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hydrocephalus (cerebral aqueduct compression)</td>
</tr>
<tr>
<td>5. Tonsillar</td>
<td>Cerebellar tonsils herniate through foramen magnum</td>
<td>Infra tentorial lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Following central tentorial herniation</td>
<td>Neck stiffness and head tilt (tonsillar impaction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Following LP in presence of intracranial mass lesion</td>
<td>Decreased LOC (midbrain compression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Flaccid paralysis</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Respiratory irregularities, respiratory arrest (compression of medullary respiratory centers)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blood pressure instability (compression of medullary cardiovascular centers)</td>
</tr>
</tbody>
</table>
Treatment of Elevated ICP

• CT or MRI to identify etiology, assess for midline shift/herniation
• treat primary cause (i.e. remove mass lesions, ensure adequate ventilation)
• if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
• goals: keep ICP <20 mmHg, CPP >65 mmHg, MAP >90 mmHg

Conservative Measures

• elevate head of bed at 30°, maintain neck in neutral position → increases intracranial venous outflow with minimal effect on arterial pressure
• prevent hypotension with fluid and vasopressors, dopamine, norepinephrine prn
• ventilate to normocarbia (pCO₂ 35-40 mmHg) → prevents vasodilatation
• oxygen to maintain pO₂ >60 mmHg prevents hypoxic brain injury
• osmolar diuresis (mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolarity of 315-320)
  ▪ can give rapidly, acts in 15-30 min, must maintain sBP >90 mmHg
• corticosteroids → decrease edema over subsequent days around brain tumor, abscess, blood
  ▪ no proven value in head injury or stroke

Aggressive Measures

• sedation (“light” e.g. barbiturates/codeine → “heavy” e.g. fentanyl/MgSO₄)
• paralysis with vecuronium → reduces sympathetic tone, reduces HTN induced by muscle contraction
• hyperventilate to pCO₂ 30-35 mmHg
  ▪ use for brief periods only – also results in decreased cerebral blood flow
• drain 3-5 mL CSF via ventricles, assess each situation independently
• insert EVD (if acute) or shunt
• barbiturate-induced coma induced with pentobarbital to reduce cerebral blood flow and metabolism (10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion)
  ▪ decreases mortality, but no improvement in neurological outcome
• decompressive craniectomy is a last resort
• no role for the use of hypothermia in head injury

Hydrocephalus

• hydrocephalus in children, see Pediatric Neurosurgery, NS36

Definition

• accumulation of excess CSF in the brain
• CSF: produced by choroid plexus lateral ventricles
• total volume ~120 mL, including 30 cc within ventricular system, remainder in SA space
• flow: lateral ventricle → 3rd ventricle → cerebral aqueduct → 4th ventricle → subarachnoid space
• re-absorbed by arachnoid villi into dural venous sinuses

Etiology

• congenital vs. acquired
• obstruction to CSF flow
• decreased CSF absorption
• increased CSF production (rarely) – e.g. choroid plexus papilloma (0.4-1% of intracranial tumors)

Epidemiology

• estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1,000 live births
Classification

Table 4. Classification of Hydrocephalus

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition</th>
<th>Etiology</th>
<th>Findings on CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive Hydrocephalus</td>
<td>Circulation blocked within ventricular system proximal to the arachnoid granulations</td>
<td>Acquired: • Aqueductal stenosis (adhesions following infection, hemorrhage)</td>
<td>Ventricular enlargement proximal to block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Intraventricular lesions (tumors e.g. 3rd ventricle colloid cyst, hematomata)</td>
<td>Periventricular hypodensity (transependymal migration of CSF forced into extracellular space)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mass causing tentorial herniation, aqueduct/4th ventricle compression</td>
<td>Sulcal effacement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Others: neurosarcoïdosis, abscess/granulomas, arachnoid cysts</td>
<td></td>
</tr>
<tr>
<td>Congenital Hydrocephalus</td>
<td></td>
<td>Acquired: • Aqueductal stenosis, Dandy-Walker malformation, Chiari malformation</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ventricular enlargement proximal to block</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Periventricular hypodensity (transependymal migration of CSF forced into extracellular space)</td>
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<td></td>
<td></td>
<td>• Sulcal effacement</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Congenital: • Aqueductal stenosis, Dandy-Walker malformation, Chiari malformation (see Pediatric Neurosurgery, NS34)</td>
<td></td>
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<td></td>
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<td>• Ventricular enlargement proximal to block</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sulcal effacement</td>
<td></td>
</tr>
<tr>
<td>Non-Obstructive (Communicating) Hydrocephalus</td>
<td>CSF absorption blocked at extraventricular site = arachnoid granulations</td>
<td>Acquired: • Post-infectious (#1 cause) meningoencephalitis, cysticercosis</td>
<td>All ventricles dilated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Post-hemorrhagic (#2 cause) SAH, NVH, traumatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Choroid plexus papilloma (rare, causes increased CSF production)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Idiopathic → normal pressure hydrocephalus</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Congenital: • Aqueductal stenosis, Dandy-Walker malformation, Chiari malformation (see Pediatric Neurosurgery, NS34)</td>
<td></td>
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<td>• Ventricular enlargement proximal to block</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sulcal effacement</td>
<td></td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus (NPH)</td>
<td>Persistent ventricular dilatation in the context of normal CSF pressure</td>
<td>Acquired: • Idiopathic (50%) Others: subarachnoid hemorrhage, meningoencephalitis, trauma, radiation-induced</td>
<td>Enlarged ventricles without increased prominence of cerebral sulci</td>
</tr>
<tr>
<td>Hydrocephalus Ex Vacuo</td>
<td>Ventricular enlargement resulting from atrophy of surrounding brain tissue</td>
<td>Acquired: • Normal aging</td>
<td>Enlarged ventricles and sulci</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alzheimer’s, Creutzfeldt-Jacob Disease</td>
<td>Cerebral atrophy</td>
</tr>
</tbody>
</table>

Clinical Features

• acute hydrocephalus
  • signs and symptoms of acute elevated ICP (see Elevated ICP, NS5)
  • impaired upward gaze (“sunset eyes”) and/or CN VI palsy
• chronic/gradual onset hydrocephalus (i.e. NPH)
  • gradual onset of classic triad developing over weeks or months
  • pressure of ventricle on lower extremity motor fibers → gait disturbance (ataxia and apraxia usually initial symptoms)
  • pressure on cortical bowel/bladder center → urinary incontinence
  • pressure on frontal lobes → dementia
• CSF pressure can be measured within clinically “normal” range

Investigations

• CT/MRI (periventricular lucency suggests raised CSF pressure)
• ultrasound (through anterior fontanelle in infants)
• ICP monitoring (e.g. LP) may be used to investigate NPH, test response to shunting (lumbar tap test)
• radionuclide cisternography can test CSF flow and absorption rate (unreliable)
• β-2 transferrin assay to test for the presence of CSF leak

Treatment

• ventricular drainage
• surgical removal of obstruction (if possible) or excision of choroid plexus papilloma
• shunts
  • ventriculoperitoneal (VP): most common
  • ventriculopleural
  • ventriculo-atrial (VA): relatively increased risk of infections, shunt emboli
• lumboperitoneal: for communicating hydrocephalus and pseudotumor cerebri
• third ventriculostomy (for obstructive hydrocephalus) via ventriculoscopy
• LPs for transient hydrocephalus (e.g. SAH), IVH in premature infants, etc.
**Table 5. Shunt Complications**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Obstruction (most common) | • Obstruction by choroid plexus  
• Buildup of proteinaceous accretions, blood, cells (inflammatory or tumor)  
• Infection  
• Disconnection or damage | • Acute hydrocephalus  
• Increased ICP | • “Shunt series” (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration)  
• CT  
• Radionuclide “shuntogram” |
| Infection (3-6%) | • S. epidermidis  
• S. aureus  
• P. acnes  
• Gram-negative bacilli | • Fever, N/V, anorexia, irritability  
• Meningitis  
• Peritonitis  
• Signs and symptoms of shunt obstruction  
• Shunt nephritis (VA shunt) | • CBC  
• Blood culture  
• Tap shunt for C&S (LP usually NOT recommended) |
| Overshunting (10% over 6.5 yr) | • Silt ventricle syndrome, collapse of ventricles leading to occlusion of shunt ports by ependymal lining  
• Subdural hematoma  
• Collapsing brain tears bridging veins (especially common in NPH patients)  
• Secondary craniosynostosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus | • Chronic or recurring H/A often relieved when lying down  
• Asymptomatic  
• H/A, vomiting, somnolence | • CT/MRI  
• Silt-like ventricles on imaging  
• CT |
| Seizures (5.5% risk in 1st yr, 1.1% after 3rd yr) | | | • EEG |
| Inguinal Hernia (17% incidence with VP shunt inserted in infancy) ± skin breakdown over hardware | • Increased intraperitoneal pressure/fluid results in hernia becoming apparent | • Inguinal swelling, discomfort | • U/S |

**Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)**

**Definition**
- raised intracranial pressure and papilledema without evidence of any mass lesion, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)

**Etiology**
- unknown (majority), but associated with
  - lateral venous sinus thrombosis
  - habitus/diet: obesity, hyper/hypovitaminosis A
  - endocrine: reproductive age, menstrual irregularities, Addison's/Cushing's disease, thyroid irregularities
  - hematological: iron deficiency anemia, polycythemia vera
  - drugs: steroid administration or withdrawal, tetracycline, nalidixic acid, etc.
- risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones ("fat, female, fertile, forties")

**Epidemiology**
- incidence ~0.5/100,000 per year
- usually in 3rd and 4th decade (F>M)

**Clinical Features**
- symptoms and signs of raised ICP (H/A in >90%, pulsatile intracranial noise), but no LOC or diplopia
- decreased visual acuity, papilledema, visual field defect, optic atrophy (key morbidity)
- usually self-limited, recurrence is common, chronic in some patients
- risk of blindness is not reliably correlated to symptoms or clinical course

**Important Features to Note on CT and MRI (± contrast enhancement)**
- Lesions (± edema, resection, hemorrhage)
- Midline shifts and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)
Investigations
- CT: normal
- CSF studies: normal
- MRI: must look for venous sinus thrombosis

Treatment
- rule out conditions that cause intracranial HTN (especially sinus thrombosis)
- discontinue offending medications, encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic, or furosemide
- if above fail: serial LPs, shunt
- optic nerve sheath decompression (if progressive impairment of visual acuity)
- 2 yr follow-up with imaging to rule out occult tumor, ophthalmology follow-up

Tumors

Classification
- primary vs. metastatic, intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, but can be devastating due to expansion of mass in fixed volume of skull (mass effect)
- malignant: implies rapid growth, invasiveness, but rarely extracranial metastasis
- types of intracranial tumors (* = most common)
  - neuroepithelial tissue
    - astrocytic tumors: astrocytoma, glioblastoma
    - oligodendrogial tumors
    - oligoastrocytic tumors
    - neuronal and mixed neuronal-glial tumors: ganglion cell tumors, cerebral neurocytomas/ neuroblastosmas
    - embryonal tumors: medulloblastoma, neuroectodermal
    - other: pineal, ependymal, and choroid plexus tumors
  - meningeal: meningiomas*, mesenchymal, hemangioblastomas
  - cranial and paraspineral nerves: schwannoma, neurofibroma
  - lymphomas and hematopoietic neoplasms
  - germ cell: germinomas, teratomas
  - pituitary adenomas*
  - sellar region: craniopharyngiomas, spindle cell oncocytoma
  - cysts: epidermoid/dermoid cysts, colloid cysts
  - local extension: chordomas, glomus jugulare tumors
  - metastatic tumors

Clinical Features
- supratentorial lesions
  - progressive neurological deficit (70%)
  - frontal lobe: hemiparesis, dysphasia, personality changes, cognitive changes
  - temporal lobe: auditory/olfactory hallucinations, memory deficits, contralateral superior quadrantanopsia

DDx for Ring Enhancing Lesion on CT with Contrast
- MAGICAL DR
- Metastases*
- Abscess*
- Glioblastoma (high grade astrocytoma)*
- Infarct
- Contusion
- AIDS (toxoplasmosis)
- Lymphoma
- Demyelination
- Resolving hematoma
(*3 most common diagnoses)

Primary Sources of Metastatic Brain Tumors
- Lung 44%
- Breast 10%
- Kidney (RCC) 7%
- GI 6%
- Melanoma 3%

Primary CNS lymphoma reported in 6-20% of HIV infected patients

Brain Metastasis
- ~1/3 of all adult brain tumors
- Well circumscribed, often at gray-white matter junction

Primary Brain Tumors
- Rarely undergo metastasis
- Adults = mostly supratentorial
- Children = mostly infratentorial
- parietal lobe: contralateral sensory or motor impairment, apraxia
- occipital lobe: contralateral visual field deficits, alexia
- H/A (50%) ± symptoms of elevated ICP (N/V, papilledema)
- seizures (25%)
- symptoms suggestive of TIA (ictal, post-ictal, occlusion of vessel by tumor cells or redo to “steal phenomenon”)
- endocrine disturbances with pituitary tumors
- rarely presents with hemorrhage
- **infratentorial lesions**
  - most commonly presents with signs of elevated ICP
    - H/A
    - N/V
    - papilledema
- diplopia (direct compression CN VI vs. indirect compression from increased ICP)
- vertigo
- ataxia (due to cerebellar lesions)
- **familial syndromes associated with CNS tumors**
  - von Hippel-Lindau (hemangioblastoma of brain, spinal cord, and eye)
  - tuberous sclerosis (giants cell astrocytoma, cortical tubers, and supraventricular nodules)
  - neurofibromatosis type 1 and 2 (astrocytoma, acoustic neuroma respectively)
  - Li-Fraumeni (astrocytoma)
  - Turcot syndrome (glioblastoma multiforme)
  - multiple endocrine neoplasia type 1 (MEN-1) (pituitary adenoma)

### Investigations
- CT, MRI, stereotactic biopsy (tissue diagnosis), metastatic workup

### Treatment
- conservative: serial Hx, Px, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce cytotoxic cerebral edema, pharmacological (see **Pituitary Adenoma**, NS13)
- surgical: total or partial excision (decompressive, palliative), shunt if hydrocephalus
- radiotherapy: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (e.g. Gamma Knife®)
- chemotherapy: e.g. alkylating agents (temozolomide)

### Table 6. Tumor Types: Age, Location

<table>
<thead>
<tr>
<th>Age</th>
<th>Supratentorial</th>
<th>Infratentorial (posterior fossa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15 yr</td>
<td>Astrocytoma (all grades) (50%)</td>
<td>Medulloblastoma (15-20%)</td>
</tr>
<tr>
<td></td>
<td>Craniopharyngioma (2-5%)</td>
<td>Cerebellar astrocytoma (15%)</td>
</tr>
<tr>
<td></td>
<td>Others: pineal region tumors, choroid plexus tumors, ganglioglioma, DNET</td>
<td>Ependymoma (9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bromastrom astrocytoma</td>
</tr>
<tr>
<td>&gt;15 yr</td>
<td>High grade astrocytoma (12-15%, e.g. GBM)</td>
<td>Metastasis</td>
</tr>
<tr>
<td></td>
<td>Metastasis (15-30%, includes infratentorial)</td>
<td>Acoustic neuroma (schwannoma) (5-10%)</td>
</tr>
<tr>
<td></td>
<td>Meningioma (15-20%)</td>
<td>Hemangioblastoma (2%)</td>
</tr>
<tr>
<td></td>
<td>Low grade astrocytoma (8%)</td>
<td>Meningioma</td>
</tr>
<tr>
<td></td>
<td>Pituitary adenoma (5-8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oligodendroglioma (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other: colloid cyst, CNS lymphoma, dermoid/epidermoid cysts</td>
<td></td>
</tr>
</tbody>
</table>

### Metastatic Tumors
- most common brain tumor seen clinically
- 15-30% of cancer patients present with cerebral metastatic tumors
- most common sources: lungs, breast
- other sources: kidney, thyroid, stomach, prostate, testis, melanoma
- hematogenous spread most common

### Location
- 80% are hemispheric, often at gray-white matter junction or junction of temporal-parietal-occipital lobes (likely emboli spreading to terminal MCA branches)

### Investigations
- identify primary tumor
  - metastatic workup (CXR, CT chest/abdo, abdominal U/S, bone scan, mammogram)
  - CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
  - MRI more sensitive, especially for posterior fossa
- consider biopsy in unusual cases, or if no primary identified

---

### Figure 9. Multiple brain metastases (see arrows)
Treatment
- medical
  - phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  - dexamethasone to reduce edema given with ranitidine
  - chemotherapy (e.g. small cell lung cancer)
- radiation
  - stereotactic radiosurgery: for discrete, deep-seated/inoperable tumors
  - multiple lesions: use WBRT; consider stereotactic radiosurgery if <3 lesions
  - post-operative WBRT is commonly used
- surgical
  - single/solitary lesions: use surgery + radiation

Prognosis
- median survival without treatment once symptomatic is ~1 mo, with optimal treatment 6-9 mo but varies depending on primary tumor type

Astrocytoma
- most common primary intra-axial brain tumor, common in 4th-6th decades

<table>
<thead>
<tr>
<th>World Health Organization (WHO)</th>
<th>Typical CT/MRI Findings</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – Pilocytic astrocytoma</td>
<td>± mass effect, ± enhancement</td>
<td>&gt;10 yr, cure if gross total resection</td>
</tr>
<tr>
<td>II – Low grade/diffuse</td>
<td>Mass effect, no enhancement</td>
<td>5 yr</td>
</tr>
<tr>
<td>III – Anaplastic</td>
<td>Complex enhancement</td>
<td>1.5-2 yr</td>
</tr>
<tr>
<td>IV – Glioblastoma multiplome (GBM)</td>
<td>Necrosis (ring enhancement)</td>
<td>12 mo, 10% at 2 yr</td>
</tr>
</tbody>
</table>

Clinical Features
- sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
- symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

Investigations
- CT/MRI with contrast: variable appearance depending on grade (see Table 8)
  - hypodense on CT, hypointense on T1 MRI, hyperintense on T2 MRI
  - low grade: most do not enhance and have calcification on CT
  - high grade: most enhance with CT contrast dye/gadolinium
- tissue biopsy: WHO grade and histology correlates with prognosis, but 25% chance of sampling error due to tumor heterogeneity

Treatment
- low grade diffuse astrocytoma
  - close follow-up, radiation, chemotherapy, and surgery all valid options
  - surgery: not curative, trend towards better outcomes
  - radiotherapy alone or post-operative prolongs survival (retrospective evidence)
  - chemotherapy: usually reserved for tumor progression
- high grade astrocytomas (anaplastic astrocytoma and GBM)
  - surgery
    - gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant temozolomide
    - except: extensive dominant lobe GBM, significant bilateral involvement, end-of-life care
  - stereotactic biopsy if resection not possible, followed by fractionated radiation with 2 cm margin
  - expectant (based on functional impairment – Karnofsky score <70; patient’s/family’s wishes)
  - aim to prolong “quality” survival
  - chemotherapy: ~20% response rate, temozolomide (agent of choice); better response to temozolomide predicted by MGMT gene hypermethylation
- multiple gliomas: WBRT ± chemotherapy

Meningioma
- most common primary intracranial tumor, arise from arachnoid membrane
- often calcified, cause hyperostosis of adjacent bone
- classically see Psammoma bodies on histology
- common locations: parasagittal convexity or falx (70%), sphenoid wing, tuberculum sellae, foramen magnum, olfactory groove
Clinical Features
- middle aged, slight female preponderance (M:F = 2:3), high progesterone receptors (increase in size with pregnancy), symptoms of increased ICP, focal deficits, usually solitary (10% multiple, likely with loss of NF2 gene/22q12 deletion)

Investigations
- CT with contrast: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed
- contrast enhanced MRI provides better detail
- angiography
  - most are supplied by external carotid feeders (meningeal vessels)
    - also assesses venous sinus involvement, "tumor blush" commonly seen (prolonged contrast image)
- octreotide scintigraphy: to establish if expression of somatostatin receptor

Treatment
- conservative management for non-progressive, asymptomatic lesions
- surgery is treatment of choice if symptomatic or progression on sequential imaging (curative if complete resection)
- SRS may be an option for lesions <3 cm
- endovascular embolization to facilitate surgery
- SRS or XRT for recurrent atypical/malignant meningiomas

Prognosis
- >90% 5 yr survival, recurrence rate variable (often ~10-20%)
- depends on extent of resection (Simpson's classification)

Vestibular Schwannoma (Acoustic Neuroma)
- slow-growing (average of 1-10 mm/yr), benign posterior fossa tumor
- arises from vestibular component of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of neurofibromatosis type II
- epidemiology: all age groups affected, peaks at 4th-6th decades

Clinical Features
- compression of structures in CPA, often CN VIII (unilateral hearing loss 98%, tinnitus, disequilibrium), followed by CN V and VII
- ataxia and raised ICP are late features

Investigations
- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/specific), CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

Treatment
- conservative: serial imaging (CT/MRI q6mo) and audiometry
- radiation: stereotactic radiosurgery or fractionated radiotherapy
- surgery if: lesion >3 cm, brainstem compression, edema, hydrocephalus
  - curable if complete resection (almost always possible)
  - operative complications: CN VII, VIII dysfunction (only significant disability if bilateral), CSF leak

Prognosis
- progressive unilateral or asymmetrical sensorineural hearing loss = acoustic neuroma until proven otherwise

Pituitary Adenoma
- primarily from anterior pituitary, 3rd-4th decades, M=F
- incidence in autopsy studies approximately 20%
- classification
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
    - most common functional: prolactinomas, adrenocorticotropic, growth-hormone producing
  - differential: parasellar tumors (e.g. craniopharyngioma, tuberculosis sellae meningioma), carotid aneurysm
Clinical Features
- mass effects
  - H/A
  - bitemporal hemianopsia (compression of optic chiasm)
  - CN III, IV, V1, V2, VI palsy (compression of cavernous sinus)
- endocrine effects
  - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
  - ACTH production: Cushing's disease, hyperpigmentation
  - GH production: acromegaly/gigantism
  - panhypopituitarism (hypothyroidism, hypoadrenalism, hypogonadism)
  - associated MEN-1 syndrome
  - diabetes insipidus
- pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
  - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, and panhypopituitarism
  - CSF rhinorrhea and seizures (rare)
  - signs and symptoms of subarachnoid hemorrhage (rare)

Investigations
- formal visual fields, CN testing
- endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose, FSH/LH, IGF-1), electrolytes, urine electrolytes, and osmolarity
- imaging (MRI with and without contrast)

Treatment
- medical
  - for apoplexy: rapid corticosteroid administration ± surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing's: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
  - endocrine replacement therapy
- surgical
  - trans-sphenoidal, trans-ethmoidal, trans-cranial approaches for non-secreting adenomas causing mass effect and Cushing/acromegaly (50% cure rate)

Pus

Sources of Pus/Infection
- four routes of microbial access to CNS
  1. hematogenous spread (most common): arterial and retrograde venous
     - adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
     - children: congenital cyanotic heart disease with R to L shunt
     - immunosuppression (AIDS – toxoplasmosis)
  2. direct implantation (dural disruption)
     - trauma
     - iatrogenic (e.g. following LP, post-operative)
     - congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site
     (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
  4. spread from PNS (e.g. viruses: rabies, herpes zoster)
- common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
  - treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
  - treatment: surgical drainage and antibiotics, 20% mortality
  - meningitis, encephalitis (see Infectious Diseases, ID19, ID20)
  - cerebral abscess

Cerebral Abscess

Definition
- pus in brain substance, surrounded by tissue reaction (capsule formation)

Etiology
- modes of spread: 10-60% of patients have no cause identified
- pathogens
  - Streptococcus (most common), often anaerobic or microaerophilic
  - Staphylococcus (penetrating injury)
  - Gram-negatives, anaerobes (Bacteroides, Fusobacterium)
  - in neonates: Proteus and Citrobacter (exclusively)
immunocompromised: fungi and protozoa (Toxoplasma, Nocardia, Candida albicans, Listeria monocytogenes, Mycobacterium, and Aspergillus)

Risk Factors
- fungal abnormalities (infection, AV fistulas; especially Osler-Weber-Rendu syndrome [i.e. hereditary hemorrhagic telangiectasia])
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess

Clinical Features
- focal neurological signs and symptoms
- H/A, decreased LOC; hemiparesis and seizures in 50%
- mass effect, increased ICP and sequelae (cranial enlargement in children)
- hemiparesis and seizures in 50%
- ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

Complications
- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

Investigations
- CT scan often first test in emergency department (see Figure 13)
- MRI
  - imaging of choice
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumor (white)
- WBC/ESR may be normal, blood cultures rarely helpful and LP contraindicated if large mass
- CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

Treatment
- aspiration ± excision and send for Gram stain, acid fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or rifampin (6-8 wk therapy)
  - revise antibiotics when C&S known
- anti-convulsants (1-2 yr)
- follow-up CT is critical (do weekly initially, more frequent if condition deteriorates)

Prognosis
- mortality with appropriate therapy ~10%, permanent deficits in ~50%

Blood

Table 8. Comparison of Epidemiology and Etiology of Intracranial Bleeds

<table>
<thead>
<tr>
<th>Types of Hematoma/Hemorrhage</th>
<th>Etiology</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>CT Features</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural Hematoma</td>
<td>Skull fracture causing middle meningeal bleed</td>
<td>M&gt;F (4:1), associated with trauma</td>
<td>Lucid interval before LOC</td>
<td>Hyperdense lenticular mass with sharp margins, usually limited by suture lines</td>
<td>Craniotomy</td>
<td>Good with prompt management (Note: respiratory arrest can occur from uncal herniation)</td>
</tr>
<tr>
<td>Acute SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, associated with trauma</td>
<td>No lucid interval, hemiparesis, papillary changes</td>
<td>Hyperdense crescentic mass, crossing suture lines</td>
<td>Craniotomy if bleed &gt;1 cm thick</td>
<td>Poor</td>
</tr>
<tr>
<td>Chronic SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, EtOH abusers, anti-coagulated</td>
<td>Often asymptomatic, minor H/A, confusion, signs of increased ICP</td>
<td>Hyperdense crescentic mass, crossing suture lines</td>
<td>Burr hole to drain; craniotomy if recurs</td>
<td>Good</td>
</tr>
<tr>
<td>SAH</td>
<td>Trauma, spontaneous (aneurysms, idiopathic, AVM)</td>
<td>Age 55-60 20% cases under age 45</td>
<td>Sudden onset thunderclap H/A, signs of increased ICP</td>
<td>Hyperdense blood in cisterns/fissures (sensitivity decreases over time)</td>
<td>Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed</td>
<td>Poor: 50% mortality 30% of survivors have moderate to severe disability</td>
</tr>
<tr>
<td>ICH</td>
<td>HTN, vascular abnormality, tumors, infections, coagulopathy</td>
<td>Age &gt;55, male, drug use (cocaaine, EtOH, amphetamine)</td>
<td>TIA-like symptoms, signs of increased ICP</td>
<td>Hyperdense intraparenchymal collection</td>
<td>Medical: decrease BP, control ICP Surgical: craniotomy</td>
<td>Poor: 44% mortality due to cerebral herniation</td>
</tr>
</tbody>
</table>
Extradural ("Epidural") Hematoma

Etiology
- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

Epidemiology
- young adult, M>F = 4:1; rare before age 2 or after age 60
- 1-4% of traumatic head injuries

Clinical Features
- classic sequence (seen in <30%): post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilatation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, aphasia, seizures, HTN, and respiratory distress
- deterioration can take hours to days

Investigations
- CT without contrast: "lenticular-shaped" usually limited by suture lines but not limited by dural attachments

Treatment
- admission, close neurological observation with serial CT indicated if all of the following are present:
  - small volume clot, minimal midline shift (MLS <5 mm), GCS >8, no focal deficit
  - otherwise, craniotomy to evacuate clot, follow up CT
- mannitol pre-operative if elevated ICP or signs of brain herniation

Prognosis
- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-operative
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)

Subdural Hematoma

ACUTE SUBDURAL HEMATOMA
- 1-2 d after bleeding onset

Etiology
- rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration

Risk Factors
- trauma, acceleration-deceleration injury, anticoagulants, alcohol, cerebral atrophy, infant head trauma (see Pediatrics)

Clinical Features
- no lucid period, signs and symptoms can include altered LOC, pupillary irregularity, hemiparesis

Investigations
- CT: hyperdense concave “crescentic” mass, crossing suture lines

Treatment
- craniotomy if clinically symptomatic, if hematoma >1 cm thick, or if MLS >5 mm (optimal if surgery <4 h from onset); otherwise observe with serial imaging

Prognosis
- poor overall since the brain parenchyma is often injured (mortality range is 50-90%, due largely to underlying brain injury)
- prognostic factors: initial GCS and neurologic status, post-operative ICP

CHRONIC SUBDURAL HEMATOMA
- ≥15 d after bleeding onset

Poor Prognostic Indicators for Epidural Hematoma
- Older age
- Low GCS on admission
- Pupillary abnormalities (especially non-reactive)
- Longer delay in obtaining surgery (if needed)
- Post-operative elevated ICP

Use of Drains vs. No Drains After Burr-Hole Evacuation of Chronic Subdural Hematoma: A Randomized Control Trial
Lancet 2009;374:1067-1073

Purpose: To examine the effect of drains on recurrence rates of chronic subdural hematoma (SDH), and clinical outcomes.

Study: RCT with 269 patients ≥18 yr of age with chronic SDH. Half of the patients were randomly assigned to receive a subdural drain and the other half no drain after evacuation.

Results: Recurrence occurred in 9.3% of people with a drain and 24% without (p=0.003; 95% CI 0.14-0.70). Although rates of complications were the same between the study groups, mortality at 6 mo was 8.6% in the group receiving a drain and 18.1% in the group not receiving a drain (p=0.042; 95% CI 0.1-0.99).

Conclusions: Use of drains after burr-hole drainage of chronic SDH is safe and associated with a reduced recurrence and mortality at 6 mo.
Etiology
- many start out as acute SDH
- blood within the subdural space evokes an inflammatory response:
  - fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot (forming a hygroma)
- course is determined by the balance of rebleeding from neomembranes and resorption of fluid

Risk Factors
- older, alcoholics, patients with CSF shunts, anticoagulants, coagulopathies

Clinical Features
- often due to minor injuries or no history of injury
- may present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ± seizures, progressive dementia, gait problem
- obtundation disproportionate to focal deficit; "the great imitator" of dementia, tumors

Investigations
- CT: hypodense (liquefied clot), crescentic mass

Treatment
- seizure prophylaxis only if post-traumatic seizure
- reverse coagulopathies
- burr hole drainage of liquefied clot indicated if symptomatic or thickness >1 cm; craniotomy if recurs more than twice

Prognosis
- good overall as brain usually undamaged, but may require repeat drainage

Cerebrovascular Disease

Ischemic Cerebral Infarction (80%)
- embolic, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc.
  (see Neurology)

Intracranial Hemorrhage (20%)
- SAH, spontaneous ICH, IVH

Figure 16. Aneurysms of the Circle of Willis

Types of Aneurysms
- Saccular
- Fusiform
- Dissecting

© Jerry Won 2014, after Kristina Neuman 2011

Figure 15. Subdural hematoma on CT

Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke
NEJM 2014;370:1091-1100
Purpose: To determine if early decompressive hemicraniectomy reduces mortality among patients >60 yr.
Study: 112 patients >60 yr (median age 70 yr) with malignant MCA infarction randomly assigned to conservative ICU treatment vs. hemicraniectomy. Endpoint was survival without severe disability (modified Rankin scale score 0-4).
Results: The proportion of patients who survived without severe disability was 38% in the hemicraniectomy group and 18% in the control group (OR 2.91, 95% CI 1.06-7.49). Modified Rankin scale scores in hemicraniectomy vs. control group in terms of percentages of patients: 0-2 (0%, 0%), 3 or moderate disability (7%, 3%), 4 or moderate severe disability (32%, 15%), 5 or severe disability (28%, 13%) and 6 or death (33%, 70%). Infections were more frequent in the hemicraniectomy group and herniation more frequent in the control group.
Conclusions: Hemicraniectomy increased survival without severe disability among patients >60 yr with a malignant MCA infarction.

Fisher Grade (SAH on CT scan)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal scan</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1 mm thick blood</td>
</tr>
<tr>
<td>3</td>
<td>&gt;1 mm thick blood</td>
</tr>
<tr>
<td>4</td>
<td>SAH + ICH or IVH</td>
</tr>
</tbody>
</table>
Subarachnoid Hemorrhage

Definition
- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

Etiology
- trauma (most common)
- spontaneous
  - ruptured aneurysms (75-80%)
  - idiopathic (14-22%)
  - AVMs (4-5%)
  - coagulopathies (iatrogenic or primary), vasculitides, tumors, cerebral artery dissections (<5%)

Epidemiology
- ~10-28/100,000 population/yr
- peak age 55-60, 20% of cases occur under age 45

Risk Factors
- HTN
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance abuse (cigarette smoking, cocaine, alcohol)
- conditions associated with high incidence of aneurysms (see Intracranial Aneurysms, NS21)

Clinical Features of Spontaneous SAH
- sudden onset (seconds) of severe "thunderclap" H/A usually following exertion and described as the "worst headache of my life" (up to 97% sensitive, 12-25% specific)
- N/V, photophobia
- meningismus (neck pain/stiffness, positive Kernig’s and Brudzinski’s sign)
- decreased LOC (due to either raised ICP, ischemia, seizure)
- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
- reactive HTN
- sentinel bleeds
  - represents undiagnosed SAH
  - SAH-like symptoms lasting <1 d ("thunderclap H/A")
  - may have blood on CT or LP
  - ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
- differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

Investigations
- non-contrast CT – for diagnosis of SAH
  - 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  - may be negative if small bleed or presentation delayed several days
  - acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
- lumbar puncture (highly sensitive) – for diagnosis of SAH if CT negative but high suspicion:
  - elevated opening pressure (>18 cmH2O)
  - bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12 h, lasts 2 wk
  - RBC count usually >100,000/mm³ without significant drop from first to last tube (in contrast to traumatic tap)
  - elevated protein due to blood breakdown products
- four vessel cerebral angiography ("gold standard" for aneurysms)
  - demonstrates source of SAH in 80-85% of cases
  - angiogram negative SAH: repeat angiogram in 7-14 d, if negative → "perimesencephalic SAH"
- MRA and CTA: sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

Hunt and Hess Grade (clinical grading scale for SAH)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Sx or mild H/A and/or mild meningismus</td>
</tr>
<tr>
<td>2</td>
<td>Grade 1 + CN palsy</td>
</tr>
<tr>
<td>3</td>
<td>Confusion/lethargy, mild hemiparesis, or aphasia</td>
</tr>
<tr>
<td>4</td>
<td>GCS &lt;15 but &gt;8, moderate-severe hemiparesis, mild rigidity</td>
</tr>
<tr>
<td>5</td>
<td>Coma (GCS &lt;9), decerebrate, moribund appearance</td>
</tr>
</tbody>
</table>

Mortality of Grade 1-2 20%, increased with grade

World Federation of Neurological Surgeons Grading of SAH

<table>
<thead>
<tr>
<th>WFNS Grade</th>
<th>GCS Score</th>
<th>Aphasia, Hemiparesis, or Hemiplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 *</td>
<td>15</td>
<td>–</td>
</tr>
<tr>
<td>1</td>
<td>13-14</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>13-14</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>7-12</td>
<td>+ or –</td>
</tr>
<tr>
<td>4</td>
<td>3-6</td>
<td>+ or –</td>
</tr>
</tbody>
</table>

*Intact aneurysm
Treatment
- admit to ICU or NICU
  - oxygen/ventilation prn
  - NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
  - aim to maintain sBP = 120-150 (balance of vasospasm prophylaxis, risk of re-bleed, risk of hypotension since CBF autoregulation impaired by SAH)
  - cardiac rhythm monitor, Foley prn, strict monitoring of ins and outs
- medications
  - IV NS with 20 mEq KCl/L at 125-150 cc/h
  - nimodipine 60 mg PO/NG q4h x 21 d for delayed cerebral ischemia neuroprotection; may discontinue earlier if patient is clinically well
  - seizure prophylaxis: levetiracetam (Keppra®) 500 mg PO/IV q12h x 1 wk
  - mild sedation prn

Complications
- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood – can lead to delayed cerebral ischemia and death
  - onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
  - clinical features (new onset ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor e.g. pronator drift)
  - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
  - “symptomatic” vasospasm in 20-30% of SAH patients
  - “radiographic” vasospasm in 30-70% of arteriograms performed 7 d following SAH
  - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
  - risk of cerebral infarct and death
  - treatment
    - hyperdynamic (“triple H”) therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
    - direct vasodilation via angioplasty or intra-arterial verapamil for refractory cases
- hydrocephalus (15-20%): due to blood obstructing arachnoid granules
  - can be acute or chronic, requires extraventricular drain (EVD) or shunt, respectively
  - neurogenic pulmonary edema
• hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECFV loss), not SIADH
• diabetes insipidus
• cardiac: arrhythmia (>50% have ECG changes), MI, CHF

**Prognosis**
• 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
• 30% of survivors have moderate to severe disability
• a major cause of mortality is rebleeding, for untreated aneurysms:
  ▪ risk of rebleed: 4% on first day, 15-20% within 2 wk, 50% by 6 mo
  ▪ if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  ▪ only prevention is early clipping or coiling of “cold” aneurysm
• rebleed risk for “perimesencephalic SAH” is approximately same as for general population

**Intracerebral Hemorrhage**

**Definition**
• hemorrhage within brain parenchyma, accounts for ~10% of strokes
• can dissect into ventricular system (IVH) or through cortical surface (SAH)

**Etiology**
• HTN (usually causes bleeds at putamen, thalamus, pons, and cerebellum)
• hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
• vascular anomalies
  ▪ aneurysm, AVMs, and other vascular malformations (see *Vascular Malformations*, NS22)
  ▪ venous sinus thrombosis
• arteriopathies (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
• tumors (1%): often malignant (e.g. GBM, lymphoma, metastases)
• drugs (amphetamine, cocaine, alcohol, anticoagulants, etc.)
• coagulopathy (iatrogenic, leukemia, TTP, aplastic anemia)
• CNS infections (fungal, granulomas, herpes simplex encephalitis)
• post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
• eclampsia
• post-operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
• idiopathic

**Epidemiology**
• 12-15 cases/100,000 population/yr

**Risk Factors**
• increasing age (mainly >55 yr)
• male gender
• HTN
• Black/Asian > Caucasian
• previous CVA of any type (23x risk)
• both acute and chronic heavy alcohol use; cocaine, amphetamines
• liver disease
• anticoagulants

**Clinical Features**
• TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
• gradual onset of symptoms over minutes-hours, usually during activity
• H/A, N/V, and decreased LOC are common
• specific symptoms/deficits depend on location of ICH

**Investigations**
• hyperdense blood on non-contrast CT
• CTA routine, if spot sign demonstrated there is high likelihood of clot growth

**Treatment**
• medical
  ▪ decrease MAP to pre-morbid level or by ~20% (target BP 140/90)
  ▪ check PTT/INR, and correct coagulopathy
  ▪ control raised ICP (see *Intracranial Pressure Dynamics*, NS4)
  ▪ levetiracetam/phenytoin for seizure prophylaxis
  ▪ follow electrolytes (SIADH common)
  ▪ angiogram to rule out vascular lesion unless >45 yr, known HTN, and putamen/thalamic/posterior fossa ICH (yield ~0%)
• surgical
  ▪ craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumor, cavernoma), ventriculostomy to treat hydrocephalus

• indications
  ▪ symptoms of raised ICP or mass effect
  ▪ rapid deterioration (especially if signs of brainstem compression)
  ▪ favorable location (e.g. cerebellar, non-dominant hemisphere)
  ▪ young patient (<50 yr)
  ▪ if tumor, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)

• contraindications
  ▪ small bleed: minimal symptoms, GCS >10
  ▪ poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
  ▪ medical reasons (e.g. very elderly, severe coagulopathy, difficult location [e.g. basal ganglia, thalamus])

Prognosis
• 30-d mortality rate 44%, mostly due to cerebral herniation
• rebleed rate 2-6%, higher if HTN poorly controlled

### Intracranial Aneurysms

#### Epidemiology
- prevalence 1-4% (20% have multiple)
- F:M; age 35-65 yr

#### Risk Factors
- autosomal dominant polycystic kidney disease (15%)
- fibromuscular dysplasia (7-21%)
- AVMs
- connective tissue diseases (Ehlers-Danlos, Marfan)
- family history
- bacterial endocarditis
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- atherosclerosis and HTN
- trauma

#### Types
(for location, see Figure 4, NS3)
- saccular (berry)
- most common type
- located at branch points of major cerebral arteries (Circle of Willis)
- 85-95% in carotid (anterior) system, 5-15% in vertebrobasilar (posterior) circulation
- fusiform
- atherosclerotic
- more common in vertebrobasilar system, rarely rupture
- infectious
- secondary to any infection of vessel wall, 20% multiple
- 60% Streptococcus and Staphylococcus
- 3-15% of patients with bacterial endocarditis

#### Table 9. Five Year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

<table>
<thead>
<tr>
<th>Size</th>
<th>Carotid</th>
<th>AC/MC/IC</th>
<th>Vertebral/PC/PComm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 mm</td>
<td>0%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>7-12 mm</td>
<td>0%</td>
<td>2.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>13-24 mm</td>
<td>3%</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
<tr>
<td>≥24 mm</td>
<td>6.4%</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>

AC = anterior cerebral/anterior communicating artery; IC = internal carotid artery; MC = middle cerebral artery; PC = posterior cerebral artery; PComm = posterior communicating artery

(Lancet 2003;362:103-110)

#### Clinical Presentation
- rupture (90%), most often SAH, but 30% ICH, 20% IVH, 3% subdural bleed
- sentinel hemorrhage (“thunderclap H/A”) → requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  ▪ internal carotid or anterior communicating aneurysm may compress:
    - the pituitary stalk or hypothalamus causing hypopituitarism
    - the optic nerve or chiasm producing a visual field defect
  ▪ basilar artery aneurysm may compress midbrain, pons (limb weakness), or CN III
  ▪ posterior communicating artery aneurysm may produce CN III palsy

---

**Risk of Recurrent Subarachnoid Hemorrhage, Death, or Dependence and Standardized Mortality Ratios after Clipping or Coiling of an Intracranial Aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): Long-Term Follow-Up**

Lancet Neurol 2008;8:427-433

**Objective:** To assess the long-term risk of death, disability, and rebleeding in patients randomly assigned to clipping or endovascular coiling after rupture of an intracranial aneurysm in the follow-up of the ISAT trial.

**Methods:** Randomized controlled trial comparing endovascular coiling treatment with craniotomy and clipping for ruptured intracranial aneurysms in 2,143 patients who were considered eligible for either modality of therapy. Annual follow-up was done for a mean length of 9 yr to assess long-term survival and dependency.

**Results:** 10 patients in the coiled group and 3 patients in the clipped group had rebleed from the original aneurysm. In patients with ruptured intracranial aneurysms suitable for both treatments, the survival rate at 5 yr after endovascular coiling was higher at 89% vs. 88% for neurosurgical clipping (relative risk 0.77; 95% CI 0.60-0.98). The likelihood of independence at 5 yr following treatment is the same for both groups (93% for clipping vs. 92% for clipping).

**Conclusions:** The risk of death at 5 yr was significantly lower in the coiled group than it was in the clipped group. There was a small increased risk of recurrent bleeding from a coiled aneurysm compared with a clipped aneurysm.
- ruptured aneurysms
- distal embolization (e.g. amaurosis fugax)
- seizures
- H/A (without hemorrhage)
- incidental CT or angiography finding (asymptomatic)

### Investigations
- CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

### Treatment
- ruptured aneurysms
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
  - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling), wrapping (last resort)
- choice of surgery vs. coiling not yet well defined, consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition. In general:
  - coiling: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
  - clipping: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoa, acute brainstem compression
- unruptured aneurysms
  - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  - no clear evidence on when to operate: need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20%-50%) vs. surgical risk (2%-5%)
- generally treat unruptured aneurysms >10 mm
- consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
- follow smaller aneurysms with serial angiography

### Types
- arteriovenous malformations (AVMs)
- cavernous malformations (= cavernomas, cavernous hemangiomas/angiomas)
- venous angioma
- capillary telangiectasias
- arteriovenous fistula (AVF) (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- "angiographically occult vascular malformations" (any type, 10% of malformations)

### Vascular Malformations

#### Definition
- tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma; usually congenital

#### Epidemiology
- prevalence ~0.14%, M:F = 2:1, average age at diagnosis = 33 yr
- 15-20% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs

#### Clinical Features
- hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections
- seizures (50%): more common with larger AVMs
- mass effect
- focal neurological signs secondary to ischemia (high flow → "steal phenomena")
- localized H/A, increased ICP
- bruit (especially with dural AVMs)
- may be asymptomatic ("silent")

#### Investigations
- MRI (flow void), MRA
- angiography (7% will also have one or more associated aneurysms)

#### Treatment
- decreases risk of future hemorrhage and seizure
  - surgical excision is treatment of choice
  - SRS (stereotactic radiosurgery) is preferred for small (<3 cm) or very deep lesions
  - endovascular embolization (glue, balloon) can be curative (5%) or used as adjuvant to surgery or SRS in larger lesions
  - conservative (e.g. palliative embolization, seizure control if necessary)

### Arteriovenous Malformations

#### Definition
- tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma; usually congenital

#### Epidemiology
- prevalence ~0.14%, M:F = 2:1, average age at diagnosis = 33 yr
- 15-20% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs

#### Clinical Features
- hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections
- seizures (50%): more common with larger AVMs
- mass effect
- focal neurological signs secondary to ischemia (high flow → "steal phenomena")
- localized H/A, increased ICP
- bruit (especially with dural AVMs)
- may be asymptomatic ("silent")

#### Investigations
- MRI (flow void), MRA
- angiography (7% will also have one or more associated aneurysms)

#### Treatment
- decreases risk of future hemorrhage and seizure
  - surgical excision is treatment of choice
  - SRS (stereotactic radiosurgery) is preferred for small (<3 cm) or very deep lesions
  - endovascular embolization (glue, balloon) can be curative (5%) or used as adjuvant to surgery or SRS in larger lesions
  - conservative (e.g. palliative embolization, seizure control if necessary)
Prognosis
- 10% mortality, 30-50% morbidity (serious neurological deficit) per bleed
- risk of major bleed in untreated AVMs: 2-4% per year

Cavernous Malformations
- benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins
- several genes now described: CCM1, CCM2, CCM3
- prevalence of 0.1-0.2%, both sporadic and hereditary forms described

Clinical Features
- seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A
- often an incidental finding
- hemorrhage risk less than AVM, usually minor bleeds

Investigations
- T2WI MRI (non-enhancing; see Figure 19) gradient echo sequencing (best for diagnosis)

Treatment
- surgical excision
  - only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions)

EXTRACRANIAL PATHOLOGY

Approach to Limb/Back Pain
- see Orthopedics

Extradural Lesion

Figure 20. Vascular supply of spinal cord
Root Compression

Differential Diagnosis
- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

Cervical Disc Syndrome

Etiology
- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C6-C7 (C7 root)

Clinical Features
- pain in arm follows nerve root distribution, worse with neck extension, ipsilateral rotation, and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

Investigations
- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- only consider EMG, nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue.

Treatment
- conservative
  - no bedrest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics, NSAIDs are more efficacious
  - avoid cervical manipulation, like traction
- surgical indications
  - anterior cervical discectomy is usual approach
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurological deficit

Prognosis
- 95% improve spontaneously in 4-8 wk

Table 10. Lateral Cervical Disc Syndromes

<table>
<thead>
<tr>
<th>Root Involved</th>
<th>C4-5</th>
<th>C5-6</th>
<th>C6-7</th>
<th>C7-T1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>2%</td>
<td>19%</td>
<td>69%</td>
<td>10%</td>
</tr>
<tr>
<td>Sensory</td>
<td>Shoulder</td>
<td>Thumb</td>
<td>Middle finger</td>
<td>Ring finger, 5th finger</td>
</tr>
<tr>
<td>Motor</td>
<td>Deltoid, biceps, supraspinatus</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Digital flexors, intrinsics</td>
</tr>
</tbody>
</table>

Cervical Stenosis (Cervical Spondylosis)

Definition
- cervical spondylosis is chronic disc degeneration and associated facet arthropathy
- resultant syndromes include mechanical neck pain, radiculopathy, myelopathy, and combinations

Epidemiology
- typically begins at age 40-50, M>E, most commonly at the C5-C6 > C6-C7 levels

Pathogenesis
- any of: disc degeneration/herniation, osteophyte formation, ossification, and hypertrophy of ligaments
- pathophysiology includes static compression, dynamic compression, and vascular compromise

Clinical Features
- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling’s test)
- occipital H/A is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder and arm pain, paresthesias and numbness
• Cervical myelopathy may be characterized by weakness (upper > lower extremity), decreased dexterity, and sensory changes
• UMN findings such as hyperreflexia, clonus, and Babinski reflex may be present
• Most worrisome complaint is lower extremity weakness (corticospinal tracts)
• Myelopathy may be associated with funicular pain, characterized by burning and stinging ± Lhermitte’s sign (lightning-like sensation down the back with neck flexion)

**Investigations**
• X-ray of cervical spine ± flexion/extension (alignment, fractures)
• MRI most useful for determination of bony anatomy (i.e. OPLL)
• EMG/nerve conduction studies reserved for peripheral nerve investigation

**Treatment**
• Decompression and stabilization need to be included in the management
• NSAIDs, moist heat, strengthening and range of motion exercises, analgesics, cervical collar, cervical traction
• Surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain

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**Lumbar Disc Syndrome**

**Etiology**
• Posterolaterally herniated disc compressed nerve root exiting below the level of the disc or the traversing nerve root
• Far lateral disc herniation compressed nerve root at the level of the disc or the exiting nerve root
• Central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

**Clinical Features**
• Initial back pain, then leg pain > back pain
• Limited back movement (especially forward flexion) due to pain
• Motor weakness, dermatomal sensory changes, decreased reflexes
• Exacerbation with valsala; relief with flexing the knee or thigh
• Nerve root tension signs
  - Straight leg raise (SLR, Lasegue’s test) or crossed SLR (pain should occur at less than 60 degrees) suggests L5, S1 root involvement
  - Femoral stretch test suggests L2, L3, or L4 root involvement

**Investigations**
• MRI is modality of choice
• X-ray spine (only to rule out other lesions), CT (bony anatomy)
• Myelogram and post-myelogram CT (only if MRI is contraindicated)

**Treatment**
• Conservative (same as cervical disc disease)
• Surgical indications
  - Same as cervical disc + cauda equina syndrome

**Prognosis**
• 95% improve spontaneously within 4 to 8 wk
• Do not follow patients with serial MRIs; clinical status is more important in guiding management

**Table 11. Lateral Lumbar Disc Syndromes**

<table>
<thead>
<tr>
<th></th>
<th>L3-4</th>
<th>L4-5</th>
<th>L5-S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root Involved</td>
<td>L4</td>
<td>L5</td>
<td>S1</td>
</tr>
<tr>
<td>Incidence</td>
<td>&lt;10%</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>Pain</td>
<td>Femoral pattern</td>
<td>Sciatic pattern</td>
<td>Sciatic pattern</td>
</tr>
<tr>
<td>Sensory</td>
<td>Medial leg</td>
<td>Dorsal foot to hallux</td>
<td>Lateral foot</td>
</tr>
<tr>
<td>Motor</td>
<td>Tibialis anterior (dorsiflexion)</td>
<td>Extensor hallucis longus (hallux extension)</td>
<td>Gastrocnemius, soleus (plantar flexion)</td>
</tr>
<tr>
<td>Reflex</td>
<td>Knee jerk</td>
<td>Medial hamstrings</td>
<td>Ankle jerk</td>
</tr>
</tbody>
</table>

---

**Figure 21. T2-weighted MRI of lumbar disc herniation**

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**Lumbar Disc Herniation: What are Reliable Criterions Indicative for Surgery?**

*Orthopedics* 2009;32:589-597

1. The only clear indication for early surgery in LDH is cauda equina syndrome.
2. Pain may also be an indication for surgery. If conservative treatment is intended, it should be considered for at least 2 mo but not beyond 1 yr if the patient shows minimal improvement, since the beneficial effects of surgery will diminish after this period.
3. The type of herniation on MRI is not relevant to the decision of whether or not to operate on patients with LDH.
4. Although paresis is often a red flag symptom for patients with LDH, neither the magnitude nor the duration of paresis should be used as an indication for early surgery.

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**Magnetic Resonance Imaging in Follow-Up Assessment of Sciatica**

*N Engl J Med* 2013;368:999-1002

*Background:* Follow-up MRI is a controversial method for monitoring sciatica in patients with known lumbar-disc herniation.

*Methods:* Participants (n=263) were recruited from a simultaneous, parallel, randomized study comparing surgery and conservative care for sciatica (the Sciatica Trial). MRI and clinical assessment were undertaken pre-treatment and 1 yr post-treatment segmentation to visualize disc herniation and evaluate outcome.

*Results:* At 1 yr, disc herniation was visible in 35% with a favorable outcome (complete, or nearly complete symptom resolution) and in 33% with an unfavorable outcome (p=0.70). A favorable outcome was reported in 83% of patients with disc herniation and 83% without disc herniation (p=0.70).

*Conclusions:* Anatomical abnormalities visible on repeated MRI 1 yr after treatment for sciatica due to lumbar-disc herniation could not distinguish patients with resolution of their symptoms from patients still experiencing symptoms.
Table 12. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Conus Medullaris Syndrome</th>
<th>Cauda Equina Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Sudden, bilateral</td>
<td>Gradual, unilateral</td>
</tr>
<tr>
<td><strong>Spontaneous Pain</strong></td>
<td>Rare, if present usually bilateral, symmetric in perineum or thighs</td>
<td>Severe, radicular type: in perineum, thighs, legs, back, or bladder</td>
</tr>
<tr>
<td><strong>Sensory Deficit</strong></td>
<td>Saddle; bilateral and symmetric; sensory dissociation</td>
<td>Saddle; no sensory dissociation; may be unilateral and asymmetric</td>
</tr>
<tr>
<td><strong>Motor Deficit</strong></td>
<td>Symmetric; paresis less marked; fasciculations may be present</td>
<td>Asymmetric; paresis more marked; atrophy may be present; fasciculations rare</td>
</tr>
<tr>
<td><strong>Reflexes</strong></td>
<td>Only ankle jerk absent (preserved knee jerk)</td>
<td>Knee and ankle jerk may be absent</td>
</tr>
<tr>
<td><strong>Autonomic Symptoms (bladder dysfunction, impotence, etc.)</strong></td>
<td>Urinary retention and atonic anal sphincter prominent early; impotence frequent</td>
<td>Sphincter dysfunction presents late; impotence less frequent</td>
</tr>
</tbody>
</table>

**Cauda Equina Syndrome**

**Etiology**
- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumor

**Clinical Features**
- usually acute (develops in less than 24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness/paraparesis in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
  - sensory
    - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
    - bilateral sensory loss or pain: depends on the level affected
    - saddle area (S2-S5) anesthesia
    - sexual dysfunction (late finding)

**Investigations**
- urgent MRI to confirm compression of S2-S3-S4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present; volumes controversial but anything over 250 cc in a healthy individual is cause for concern

**Treatment**
- surgical decompression (<48 h) to preserve bowel, bladder, and sexual function, and/or to prevent progression to paraplegia

**Prognosis**
- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

**Lumbar Spinal Stenosis**

**Etiology**
- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

**Clinical Features**
- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

**Investigations**
- MRI is the optimal investigation to confirm and localize the level of stenosis (unlike nerve root compression which can be localized with clinical exam)

**Treatment**
- conservative: NSAIDs, analgesia
- surgical: laminectomy with root decompression (the role of fusion may need to be considered if the amount of bone removed with the laminectomy results in de-stabilization)
Neurogenic Claudication

Etiology
- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

Clinical Features
- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

Investigations
- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

Treatment
- same as for lumbar spinal stenosis

Intradural Intramedullary Lesions

Syringomyelia (Syrinx)

Definition
- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over months to years
- initially pain, weakness, later atrophy and loss of pain and temperature sensation

Etiology
- 70% are associated with Chiari I malformation, 10% with basilar invagination
- post-traumatic
- tumor
- tethered cord

Clinical Features
- nonspecific features for any intramedullary spinal cord pathology
  - initially pain, weakness, atrophy, loss of pain and temperature in upper extremities (central syrinx) with progressive myelopathy over years
  - sensory loss with preserved touch and proprioception in a band-like distribution at the level of cervical syrinx
  - sensory loss with preserved touch and proprioception in a band-like distribution at the level of cervical syrinx
  - dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - painless neuropathic arthropathies (Charcot’s joints), especially in the shoulder and neck due to loss of pain and temperature sensation

Investigations
- MRI is best method, myelogram with delayed CT

Treatment
- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumor if causing a syrinx)
- rarely does the syrinx need to be shunted, only when progressive and size allows for insertion of tube

Spinal Cord Syndromes

- spinal cord injury impairment classified according to ASIA score
- ASIA A: complete, no motor/sensory below neurological level including S4/5
- ASIA B: incomplete, sensory but not motor function preserved below neurological level including S4/5
• ASIA C: incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade <3
• ASIA D: incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade 3 or more
• ASIA E: normal motor and sensory function

Complete Spinal Cord Lesion
• bilateral loss of motor/sensory and autonomic function at ≥4 segments below lesion/injury, with UMN signs
• about 3% of patients with complete injuries will develop some recovery within 24 h, beyond 24 h, no distal function will recover

Incomplete Spinal Cord Lesion
• any residual function at ≥4 segments below lesion
• signs include sensory/motor function in lower limbs and "sacral sparing" (perianal sensation, voluntary rectal sphincter contraction)

Table 13. Comparison Between Incomplete Spinal Cord Lesion Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Etiology</th>
<th>Motor</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown-Séquard</td>
<td>Hemisection of cord</td>
<td>Ipsilateral LMN weakness at the lesion</td>
<td>Ipsilateral loss of vibration and proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral UMN weakness below the lesion</td>
<td>Contralateral loss of pain and temperature</td>
</tr>
<tr>
<td>Anterior Cord</td>
<td>Anterior spinal artery compression or occlusion</td>
<td>Bilateral LMN weakness at the lesion</td>
<td>Preserved vibration and proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bilateral UMN weakness below the lesion</td>
<td>Bilateral loss of pain and temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary retention</td>
<td>Preserved light touch</td>
</tr>
<tr>
<td>Central Cord</td>
<td>Syringomyelia, tumors, spinal hyperextension injury</td>
<td>Bilateral motor weakness: Upper limb weakness (LMN lesion) &gt; Lower limb weakness (UMN lesion)</td>
<td>Variable bilateral suspended sensory loss Loss of pain and temperature &gt; loss of vibration and proprioception</td>
</tr>
<tr>
<td>(most common)</td>
<td></td>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td>Posterior Cord</td>
<td>Posterior spinal artery infarction, trauma</td>
<td>Preserved</td>
<td>Bilateral loss of vibration, proprioception, light touch at and below the lesion Preserved pain and temperature</td>
</tr>
</tbody>
</table>

Peripheral Nerves

• see Neurology, N35

Seddon's Classification of Peripheral Nerve Injury
• class I: neuapraxia – axon structurally intact but fails to function; recovery within hours to months (average 6-8 wk)
• class II: axonotmesis – axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury → spontaneous axonal recovery at 1 mm/d, max at 1-2 yr
• class III: neurotmesis – nerve completely transected, need surgical repair for possibility of recovery
• etiologies: ischemia, nerve entrapment – nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve

Investigations
• neurological exam (power, sensation, reflexes), localization via Tinel's sign (paresthesias elicited by tapping along the course of a nerve)
• electrophysiological studies (EMG, nerve conduction study) may be helpful in assessing nerve integrity and monitoring recovery, not helpful until 2-3 wk post-injury
• labs: blood work, CSF
• imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography
• angiogram if vascular damage is suspected

Treatment
• early neurosurgical consultation if injury is suspected
• entrapment
  • conservative: prevent repeated stress/injury, physiotherapy, NSAIDs, local anesthesia/steroid injection
  • surgical: nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management
• stretch/contusion
  • follow-up clinically for recovery; exploration if no recovery in 3 mo
• axonotmesis
  • if no evidence of recovery, resect damaged segment
prompt physical therapy and rehabilitation to increase muscle function, maintain joint range of motion, and maximize return of useful function
• recovery usually incomplete
• neurotmesis
• surgical repair of nerve sheath unless known to be intact (suture nerve sheaths directly if ends approximate or nerve graft [usually sural nerve])
• clean laceration: early exploration and repair
• contamination or associated injuries: tag initially with nonabsorbable suture, reapproach within 10 d

Complications
• neuropathic pain: with neuraoma formation
• complex regional pain syndrome: with sympathetic nervous system involvement

SPECIALTY TOPICS

Neurotrauma

Trauma Management (see Emergency Medicine, ER7)

Indications for Intubation in Trauma
1. depressed LOC (patient cannot protect airway): usually GCS ≤8
2. need for hyperventilation
3. severe maxillofacial trauma; patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management
   • if basilar skull fracture suspected, avoid nasotracheal intubation as may inadvertently enter brain
   • note: intubation prevents patient's ability to verbalize for determining GCS

Trauma Assessment

INITIAL MANAGEMENT

ABCs of Trauma Management
• see Emergency Medicine, ER2

NEUROLOGICAL ASSESSMENT

Mini-History
• period of LOC, post-traumatic amnesia, loss of sensation/function, type of injury/accident

Neurological Exam
• GCS
• head and neck (lacerations, bruises, basilar skull fracture signs, facial fractures, foreign bodies)
• spine (palpable deformity, midline pain/tenderness)
• eyes (pupillary size and reactivity)
• brainstem (breathing pattern, CN palsies)
• cranial nerve exam
• motor exam, sensory exam (only if GCS is 15), reflexes
• sphincter tone
• record and repeat neurological exam at regular intervals

Investigations
• spinal injury precautions (cervical collar) are continued until C-spine is cleared
• C.EL/spine x-rays
  • AP, lateral, odontoid views for C-spine (must see from C1 to T1; swimmer's view if necessary) or CT
  • rarely done: oblique views looking for pars interarticularis fracture ("Scottie dog" sign)
• CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
• cross and type, ABG, CBC, drug screen (especially alcohol)
• chest and pelvic x-ray as indicated

TREATMENT

Treatment for Minor Head Injury
• observation over 24-48 h
• wake every hour
• judicious use of sedatives or pain killers during monitoring period
Treatment for Severe Head Injury (GCS ≤8)
- clear airway and ensure breathing (if GCS ≤8, intubate)
- secure C-spine
- maintain adequate BP
- monitor for clinical deterioration
- monitor and manage increased ICP if present (see Herniation Syndromes, NS6)

Admission required if:
- skull fracture (indirect signs of basal skull fracture, see Head Injury)
- confusion, impaired consciousness, concussion with >5 min amnesia
- focal neurological signs, extreme H/A, vomiting, seizures
- unstable spine
- use of alcohol
- poor social support

Head Injury

Epidemiology
- M:F = 2-3:1

Pathogenesis
- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/ mesencephalic hematoma
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

Scalp Injury
- rich blood supply
- considerable blood loss (vessels contract poorly when ruptured)
- minimal risk of infection due to rich vascularity

Skull Fractures
- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
  - internal fractures into sinus may lead to meningitis, pneumocephalus
  - risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray, rely on clinical signs
  - retroauricular ecchymoses (Battle's sign)
  - peri-orbital ecchymoses (raccoon eyes)
  - hemotympanum
- CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

Cranial Nerve Injury
- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VIII: repair of ossicles
- CN injuries that improve
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
  - CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

Arterial Injury
- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

Intracranial Bleeding
- see Blood, NS15 and Cerebrovascular Disease, NS17
Brain Injury

Primary Impact Injury
- mechanism of injury determines pathology: penetrating injuries, direct impact
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- concussion: a trauma-induced alteration in mental status
  - American Academy of Neurology (AAN) Classification
    - no parenchymal abnormalities on CT
- coup (damage at site of blow) and contre-coup (damage at opposite site of blow)
  - acute decompression causes cavitation followed by a wave of acute compression
- contusion (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space-occupying lesion on CT

Secondary Pathologic Processes
- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to
  - high glutamate release → NMDA receptor activation → cytotoxic cascade
  - cerebral edema
  - intracranial hemorrhages
  - ischemia/infarction
  - raised ICP, intracranial HTN
  - hydrocephalus

Extracranial Conditions
- hypoxemia
  - due to trauma to the chest, upper airway, brainstem
  - extremely damaging to vulnerable brain cells
  - leads to ischemia, raised ICP
- hypercarbia
  - leads to raised ICP (secondary to vasodilation)
- systemic hypotension
  - caused by blood loss (e.g. ruptured spleen)
  - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
  - leads to increased brain metabolic demands → ischemia
- fluid and electrolyte imbalance
  - iatrogenic (most common)
  - SIADH caused by head injury
  - diabetes insipidus (DI)
  - may lead to cerebral edema and raised ICP
- coagulopathy

Intracranial Conditions
- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

Brain Injury Outcomes
  - nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
- moderately traumatic (GCS 9-12): proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

Late Complications of Head/Brain Injury
- seizures: 5% of head injury patients develop seizures
  - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
  - post-traumatic seizure may be immediate, early, or late
  - presence of early (within first wk) post-traumatic seizure raises incidence of late seizures
• meningitis: associated with CSF leak from nose or ear
• hydrocephalus: acute hydrocephalus or delayed normal pressure hydrocephalus (NPH)

### Spinal Cord Injury

- see **Orthopedics, OR21** and **Emergency Medicine, ER9**

#### Neurogenic and Spinal Shock

1. neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by:
   - interruption of sympathetics (unopposed parasympathetics) below the level of injury
   - loss of muscle tone due to skeletal muscle paralysis below level of injury → venous pooling
   - blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the spinal cord injury, causing flaccid paralysis and areflexia for variable periods

#### Whiplash-Associated Disorders

- definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck

#### Initial Management of SCI

- major causes of death in SCI are aspiration and shock
- the following patients should be treated as having a SCI until proven otherwise:
  - all victims of significant trauma
  - minor trauma patients with decreased LOC or complaints of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

#### Stabilization and Initial Evaluation in the Hospital

1. ABCs, immobilization (backboard/head strap), oxygenation, Foley catheter to urometer, temperature regulation
2. hypotension: maintain sBP >90 mmHg with pressors (dopamine), hydration, and atropine
   - DVT prophylaxis
3. monitor CBC/electrolytes
4. focused history (see **Trauma Assessment, NS29**)
5. spine palpation: point tenderness or deformity
6. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
7. sensory level assessment: pinprick, light touch, and proprioception
8. evaluation of reflexes
9. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
10. radiographic evaluation
   - 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction
   - flexion-extension views to disclose occult instability
   - CT scan (bony injuries) typically most trauma centers use CT as the modality of choice for looking at fractures, very sensitive with the high resolution scanners
   - MRI mandatory if neurological deficits (soft tissue injuries)

#### Medical Management Specific to SCI

- option: methylprednisolone (given within 8 h of injury) this is controversial and you need to confer with Neurosurgery service
- ± decompression in acute, non-penetrating SCI

### Fractures of the Spine

#### Fractures and Fracture-Dislocations of the Thoracic and Lumbar Spine

- assess ligamentous instability using flexion/extension x-ray views of C-spine ± MRI
- thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
- anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
- middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
- posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous, and ligamentum flavum ligaments

#### Types of Injury (Denis Classification)

- compression fracture
  - produced by flexion
posterior ligament complex (supraspinous and interspinous ligaments, ligamentum flavum, and intervertebral joint capsules) remain intact

- fractures are stable but lead to kyphotic deformity

**burst fracture**
- stable: anterior and middle columns parted with bone retropulsed nearby
  - hallmark is pedicle widening on AP x-ray
  - spinal cord (seen on x-ray and CT); posterior column is uninjured
- unstable: same as the stable but with posterior column disruption (usually ligamentous)

**flexion distraction injury**
- hyperflexion and distraction of posterior elements
  - middle and posterior columns fail in distraction
- classic: Chance = horizontal fracture through posterior arch, pedicles, posterior vertebral body
  - can be purely ligamentous, i.e. through PLL and disc

**fracture-dislocation**
- anterior and cranial dislocation of superior vertebral body → 3 column failure
  - three types:
    - flexion-rotation
    - flexion-distraction
    - shear/hyperextension (rare)

Management of Thoracolumbar Injury
- management based on TLICS classification

**FRACTURES OF THE CERVICAL SPINE**

**Types of Injury**
- C1 vertebral fracture (Jefferson fracture)
  - vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing the lateral masses of the atlas outward and disrupting the ring of the atlas
  - also can cause an occipital condylar fracture
- odontoid process fracture
  - causes C1 and odontoid of C2 to move independently of C2 body
  - this occurs because
    - normally C1 vertebra and odontoid of C2 are a single functional unit
    - alar and transverse ligaments on posterior aspect of odontoid most commonly remain intact following injury
  - patients often report a feeling of instability and present holding their head with their hands
- C2 vertebral fracture (hangman fracture, traumatic spondylolisthesis of axis):
  - bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3
  - usually neurologically intact
- Clay-Shoveler fracture
  - avulsion of spinous process, usually C6 or C7

**Imaging**
- AP spine x-ray (open-mouth and lateral view), CT

**Treatment**
- immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
- Type II and III odontoid fractures
  - consider surgical fixation for comminution, displacement, or inability to maintain alignment with external immobilization
  - confirm stability after recovery with flexion-extension x-rays

---

**Neurologically Determined Death**

**Definition**
- irreversible and diffuse brain injury resulting in absence of clinical brain function
- cardiovascular activity may persist for up to 2 wk

**Criteria of Diagnosis**
- prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature >32°C, no electrolyte/acid-base/endocrine disturbance
- absent brainstem reflexes
  - absent pupillary light reflex
  - absent corneal reflexes
  - absent oculocephalic response
- absent caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides)
Coma

Definition
- an unrousable state in which patients show no meaningful response to environmental stimuli

Pathophysiology
- lesions affecting the cerebral cortex bilaterally, the reticular activating system (RAS) or their connecting fibers
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

Classification
- structural lesions (tumor, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B₁₂)
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
  - infections (meningitis, encephalitis)
  - trauma (concussion, diffuse shear axonal damage)

Investigations and Management
- ABCs
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP, EEG

Persistent Vegetative State

Definition
- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- "awake but not aware"
- follows comatose state

Etiology/Prognosis
- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

Pediatric Neurosurgery

Spinal Dysraphism

SPINA BIFIDA OCCULTA

Definition
- congenital absence of a spinous process and a variable amount of lamina
- no visible exposure of meninges or neural tissue

Epidemiology
- 15-20% of the general population; most common at L5 or S1

Etiology
- failure of fusion of the posterior neural arch
Clinical Features
- no obvious clinical signs
- presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia)

Investigations
- plain film: absence of the spinous process along with minor amounts of the neural arch
- U/S, MRI to exclude spinal anomalies

Treatment
- requires no treatment

MENINGOCELE (SPINA BIFIDA APERTA)

Definition
- herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue

Etiology
- primary failure of neural tube closure

Clinical Features
- most common in lumbosacral area
- usually no disability, low incidence of associated anomalies, and hydrocephalus

Investigations
- plain films, CT, MRI, U/S, echo, GU investigations

Treatment
- surgical excision and tissue repair (excellent results)

MYELOMENINGOCELE (SPINA BIFIDA APERTA)

Definition
- herniation of meningeal and CNS tissue through a defect in the spine

Etiology
- same as meningocele

Clinical Features
- sensory and motor changes distal to anatomic level producing varying degrees of weakness
- urinary and fecal incontinence
- 65-85% of patients with myelomeningocele have hydrocephalus
- most have Type II Chiari malformation (see Chiari Malformations, NS36)

Investigations
- plain films, CT, MRI, U/S, echo, GU investigations

Treatment
- surgical closure to preserve neurologic status and prevent CNS infections
- closure in utero shown to decrease hydrocephalus and improve post natal motor scores

Prognosis
- operative mortality close to 0%, 95% 2 yr survival
- 80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence
- early mortality usually due to Chiari malformation complications (respiratory arrest and aspiration), whereas late mortality is due to shunt malfunction

Intraventricular Hemorrhage
- see Pediatrics, P72
Hydrocephalus in Pediatrics

Etiology
- congenital
  - aqueductal anomalies, primary aqueductal stenosis in infancy
  - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  - Dandy-Walker malformation (2-4%)
  - Chiari malformation, especially Type II
  - myelomeningocele
- acquired
  - post meningitis
  - post hemorrhage (SAH, IVH)
  - masses (vascular malformation, neoplastic)

Clinical Features
- symptoms and signs of hydrocephalus are age related in pediatrics
- increased head circumference (HC), bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding, and vomiting
- "cracked pot" sound on cranial percussion
- scalp vein dilation (increased collateral venous drainage)
- sunset sign – forced downward deviation of eyes
- episodic bradycardia and apnea

Investigations
- skull x-ray, U/S, CT, MRI, ICP monitoring

Treatment
- similar to adults (see Hydrocephalus, NS7)

Dandy-Walker Malformation

Definition
- atresia of foramina of Magendie and Luschka, resulting in
  - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic
cerebellar hemispheres
  - posterior fossa cyst, enlarged posterior fossa
  - dilatation of 4th ventricle (also 3rd and lateral ventricles)
- associated anomalies
  - hydrocephalus (90%)
  - agenesis of corpus callosum (17%)
  - occipital encephalocele (7%)

Epidemiology
- 2-4% of pediatric hydrocephalus

Clinical Features
- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

Investigations
- ultrasound, CT, MRI

Treatment
- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
  - e.g. ventriculoperitoneal (VP) shunt, cystoperitoneal (CP) shunt, lumboperitoneal (LP)
  - shunt, ventriculoatrial (VA) shunt, lumbar drain

Prognosis
- 75-100% survival, 50% have normal IQ

Chiari Malformations

Definition
- malformations at the medullary-spinal junction

Etiology
- unclear, likely maldevelopment/dysgenesis during fetal life
Categories

- Type I (cerebellar ectopia)
  - definition: cerebellar tonsils lie below the level of the foramen magnum
  - epidemiology: average age at presentation 15 yr
  - clinical features:
    - many are asymptomatic
    - scoliosis
    - brain compression
    - central cord syndrome (65%)
    - syringomyelia (50%)
    - foramen magnum compression syndrome (22%)
    - cerebellar syndrome (11%)
    - hydrocephalus (10%)

- Type II
  - definition: part of cerebellar vermis, medulla, and 4th ventricle extend through the foramen magnum often to midcervical region
  - almost always associated with a myelomingocele
  - epidemiology: present in infancy
  - clinical features: findings due to brainstem and lower cranial nerve dysfunction
  - syringomyelia, hydrocephalus in >80%

Investigations

- MRI

Treatment

- indications for surgical decompression
  - Type I: symptomatic patients (early surgery recommended; <2 yr post symptom onset) → suboccipital craniectomy, duraplasty
  - Type II: neurogenic dysphagia, stridor, apneic spells → cervical laminectomy, duraplasty

Craniosynostosis

**Definition**

- premature closure of the cranial suture(s)

**Classification**

- sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
- coronal: expansion in superior and lateral direction (brachiocephaly)
- metopic (trigonocephaly)
- lambdoid: least common

**Epidemiology**

- 0.6/1,000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

**Clinical Features**

- skull deformity, raised ICP ± hydrocephalus
- ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
- must differentiate between positional plagiocephaly (secondary to back sleeping)

**Investigations**

- plain radiographs, CT scan

**Treatment**

- parental counseling about nature of deformity, associated neurological symptoms
- surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

Pediatric Brain Tumors

- see Tumors, NS10

**Epidemiology**

- 20% of all pediatric cancers (second only to leukemia)
- 60% of pediatric brain tumors are infratentorial
- pediatric brain tumors arise from various cellular lineages
  - glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see Astrocytoma, NS12)
  - primitive nerve cells: supratentorial PNET
    - 90% of neonatal brain tumors, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
  - non-neuronal cells: germ cell tumor, craniopharyngioma, dermoid, meningioma, neurinoma (schwanoma), pituitary adenoma, others
Clinical Features
- vomiting, seizure, macrocrania, hydrocephalus
- developmental delay, poor feeding, failure to thrive
- often initially escapes diagnosis due to expansive cranium and neural plasticity in children

Table 14. Overview of Childhood Primary Brain Tumors

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<tr>
<th>Tumor Type</th>
<th>Clinical Characteristics</th>
<th>Notes</th>
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</thead>
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<tr>
<td>Pilocytic (low grade) Astrocytoma</td>
<td>Usually in posterior fossa</td>
<td>Well circumscribed, good prognosis</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>A primitive neuroectodermal tumor (PNET)</td>
<td>In cerebellum → compresses 4th ventricle → hydrocephalus</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>In 4th ventricle → hydrocephalus</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>Often cerebellar</td>
<td>Associated with von Hippel-Lindau syndrome with retinal angiomas</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Causes bitemporal hemianopsia (thus often confused with pituitary adenoma)</td>
<td>Most common supratentorial childhood tumor</td>
</tr>
</tbody>
</table>

Most Common Pediatric Brain Tumors
Astrocytoma, low grade
Supratentorial
Infratentorial
Medulloblastoma
Ependymoma
Glioblastoma

Rickard CR, Paulus W. Epidemiology of central nervous system tumors in childhood and adolescence based on the new WHO classification. Childs Nerv Syst 2011;27(9):903-911

Functional Neurosurgery

Movement Disorders
- see Neurology, Tremor, Parkinson’s Disease, Dystonia, and Multiple Sclerosis sections in, N28, N30, N32, N52, respectively

Table 15. Surgical Targets for Movement Disorders

<table>
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<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td>Intractable contralateral bradykinesia/tremor</td>
<td>Simultaneous, bilateral surgery/stimulation is most common Preferred target: anterodorsal subthalamic nucleus (STN) Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus pars interna (GPi) Caudal zona incerta Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus</td>
<td>39-48% improvement in Unified Parkinson’s Disease Rating Scale (UPDRS) scores Reduced dosage of medications (STN) More effective than medical management in advanced PD Early intervention may reduce severity, course, and progression of disease Of little benefit for patients with atypical presentations</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias Involuntary movements Cognitive functioning: decreased lexical fluency, impaired executive function (STN &gt; GPi) Psychiatric: depression, mania, anxiety, apathy (STN &gt; GPi)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Contralateral primary dystonia; cervical and tardive dystonias (see dystonia, below)</td>
<td>Preferred target (primary dystonia): stereotactic ablation (pallidotomy)/stimulation of anterodorsal STN Secondary dystonia: stimulation of posteroventral GPi</td>
<td>Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDS) score Secondary dystonia: 62-89% improvement in dystonias Delayed effects: weeks → months</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%) Minor effects on cognitive functioning (especially decreased lexical fluency; STN &gt; GPi)</td>
</tr>
<tr>
<td>Tremor</td>
<td>Contralateral appendicular ET (first disorder to be treated by DBS; DBS is viable alternative to Rx) Intention tremor (IT) resulting from denervation of cerebellar outflow tracts (e.g. in multiple sclerosis) Brainstem tremor</td>
<td>Preferred target: stereotactic ablation (thalamotomy)/stimulation of Vim nucleus of thalamus Other targets: stimulation of caudal zona incerta Parkinsonian tremor: stimulation of anterodorsal STN</td>
<td>Durable reductions in essential tremor rating scale (ETRS) scores Reduced dosage of medications Conflicting data on vocal/facial tremor</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias/pain Dysarthria Ataxia Minor effects on cognitive functioning (especially decreased lexical fluency) Tolerance may develop over time</td>
</tr>
</tbody>
</table>
Neuropsychiatric Disorders

- see Neurology, N33 and Psychiatry, PS13, PS7 for Tourette's Syndrome, Obsessive Compulsive Disorder and Depression

Table 16. Surgical Targets for Neuropsychiatric Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive Compulsive Disorder (OCD)</td>
<td>Severe symptoms refractory to medical management</td>
<td>Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC)</td>
<td>Currently under investigation</td>
<td>Intracerebral hemorrhages (1-2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reported 25-75% response rate</td>
<td></td>
<td>Mild effects on cognitive functioning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety ± panic disorder</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracerebral hemorrhages (1-2%) Mild sexual dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tourette's Syndrome</td>
<td>Severe symptoms refractory to medical management</td>
<td>Stimulation of midline intralaminar nuclei of the thalamus</td>
<td>Currently under investigation</td>
<td>Intracerebral hemorrhages (1-2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulation of motor and limbic portions of GPi</td>
<td>Reported &gt;70% reduction in vocal or motor tics + urge</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stimulation of the anterior limb of the IC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Depressive Disorder (MDD)</td>
<td>Severe depression refractory to medical management and ECT</td>
<td>Stimulation of the subgenual cingulate cortex</td>
<td>Currently under investigation</td>
<td>Intracerebral hemorrhages (1-2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reported 60% response rate; 35% remission rate</td>
<td></td>
<td>Pain, H/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxiety ± panic disorder</td>
<td></td>
<td>Worsening mood, irritability</td>
</tr>
</tbody>
</table>

Chronic Pain

Table 17. Surgical Targets for Chronic Pain

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain</td>
<td>Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, complex regional pain syndrome)</td>
<td>Preferred target: stimulation of the contralateral VPL, VPM thalamic nuclei ± periventricular/periaqueductal gray matter (PVG/PAG) Other targets: stimulation of the contralateral IC</td>
<td>47% improvement in perception of pain intensity</td>
<td>Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder</td>
</tr>
<tr>
<td>Nociceptive Pain</td>
<td>Severe, intractable, organic nociceptive pain</td>
<td>Bilateral (most common) stimulation of the PVG/PAG</td>
<td>Reportedly 63% improvement in perception of pain intensity</td>
<td>Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder</td>
</tr>
</tbody>
</table>

Surgical Management of Epilepsy

- see Neurology, N16 for the medical treatment of epilepsy

Indications
- medically refractory seizures, usually defined as seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing; other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

Procedure
- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common

Outcomes
- 41-79% of adult patients are seizure free for 5 yr after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

Morbidity
- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anteromedial temporal lobectomies
most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
the degree of memory decline stabilizes after 1-2 yr

Predictors
positive predictive factors for seizure freedom following anteromedial temporal lobectomy
- hippocampal sclerosis (unilateral)
- focal localization of interictal epileptiform discharges
- absence of pre-operative generalized seizures
- tumoral cause
- complete resection of the lesion
- SES

Surgical Management for Trigeminal Neuralgia
reserved for cases refractory to medical management; see Neurology, N8 for medical management

Surgical Options
trigeminal nerve branch procedures
- local blocks (phenol, alcohol)
- neurectomy of the trigeminal branch
neural branches
- V1: block at the supraorbital, supratrochlear nerves
- V2: block at the foramen rotundum or infraorbital nerves
- V3: block at the foramen ovale
percutaneous trigeminal rhizotomy
- glycerol injection
- mechanotrauma via catheter balloon
- radiofrequency thermocoagulation
- Gamma Knife® radiosurgery
- microvascular decompression
- posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable 'Tellon' felt

Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Common Interactions</th>
<th>Contraindications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>lorazepam</td>
<td>4 mg IV over 2 min, q10-15min (do not exceed 8 mg/12h)</td>
<td>Status epileptic</td>
<td>Drowsiness, sedation</td>
<td>Other CNS depressants, digoxin (increases digoxin levels)</td>
<td></td>
<td>Start phenytoin loading simultaneously</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>Trigeminal neuralgia (tic douloureux): 100 mg PO bid, increase by 200 mg/d up to a maximum of 1,200 mg/d</td>
<td>Trigeminal neuralgia</td>
<td>Worsening of seizures, heart failure, arrhythmias, AV block, aplastic anemia, agranulocytosis, thrombocytopenia, hepatitis, erythema multiforme, Stevens-Johnson syndrome</td>
<td>Lithium (increases lithium toxicity), MAOI</td>
<td>Other meds may increase carbamazepine levels or have decreased effects</td>
<td>Hypersensitivity to TCAs, previous bone marrow suppression, MAOI in past 14 d</td>
</tr>
<tr>
<td>phenytoin</td>
<td>Seizures: Loading dose: 18 mg/kg slow IV or 300-600 mg PO/d divided bid/tid</td>
<td>Status epileptic</td>
<td>Thrombocytopenia, leukopenia, agranulocytosis, pancytopenia, toxic hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis</td>
<td>Other meds may increase phenytoin levels and toxicity or have decreased effects</td>
<td>Bradyarrhythmias, heart block</td>
<td>Important to give over time to prevent causing a cardiac arrest</td>
</tr>
</tbody>
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Table 18. Common Medications (continued)

<table>
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<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Common Interactions</th>
<th>Contraindications</th>
<th>Comments</th>
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<tr>
<td>dexamethasone</td>
<td>Loading dose: 10-20 mg IV/Maintenance: 4-6 mg IV/d divided qid (may be PO)</td>
<td>Cerebral edema (e.g. secondary to tumor, head injury, pseudotumor cerebri) Pre-operative preparation for patients with increased ICP secondary to brain neoplasms</td>
<td>Seizures, heart failure, arthriticms, thromboembolism, pancreatitis, acute renal insufficiency; avoid abrupt withdrawal</td>
<td>Aminoglycosides, antibiotics, ASA, NSAIDs, barbituates, phenytoin, rifampin, cardiac glycosides, cyclosporine, epididym, oral anticoagulants, potassium-depleting drugs, salicylates, skin-testing antigens, toxoids, vaccines</td>
<td>Systemic fungal infections; immunosuppressive dose with live virus vaccines</td>
<td>No longer used in acute spinal cord injury</td>
</tr>
<tr>
<td>nimodipine</td>
<td>60 mg PO/NG q4h x 21 d started within 96 h of SAH</td>
<td>Vasospasm in SAH</td>
<td>Decreased blood pressure, tachycardia, dyspnea</td>
<td>Antihypertensives (may increase hypotensive effects), CCB (may increase effects), cimetidine (increases nimodipine bioavailability)</td>
<td>None known</td>
<td>Causes vasodilation Only calcium channel blocker that crosses blood brain barrier Use half the normal dose for liver failure; monitor BP always</td>
</tr>
</tbody>
</table>


# Obstetrics

**Meg Casson, Anna Ly, and Anna Mackenzie**, chapter editors  
**Khaled Ramadan, Karim Virani, and Vahagn Karapetyan**, associate editors  
**Alexa Bramall**, EBM editor  
**Dr. Eva Mocarski, Dr. Amanda Selk, and Dr. Rajiv Shah**, staff editors

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<td>Abnormal Progression of Labor (Dystocia)</td>
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<td>Shoulder Dystocia</td>
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<td>Umbilical Cord Prolapse</td>
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<td>Lacerations</td>
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<td>Uterine Inversion</td>
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<td>Postpartum Pyrexia</td>
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<td>Mastitis</td>
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<td>Postpartum Mood Alterations</td>
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<td>Common Medications</td>
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<td>References</td>
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Placenta
- site of fetal nutritive, respiratory, and excretory function
- discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- produces hormones such as progesterone, placental lactogen, estrogen, relaxin, β-hCG, and IGFs
- poor implantation can lead to spontaneous abortion
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see Antepartum Hemorrhage, OB24)

Pregnancy

Diagnosis of Pregnancy

History
- obstetrical and gynecological history
- obtain the year, location, mode of delivery, duration of labor, sex, gestational age, birth weight, and complications of every pregnancy; organize into GTPAL format
  - Gravidity (G)
    - G: total number of pregnancies of any gestation
    - includes current pregnancy, abortions, ectopic pregnancies, and hydatidiform moles (multiple gestation = one pregnancy)
  - Parity (TPAL)
    - T: number of term infants delivered (>37 wk)
    - P: number of premature infants delivered (20-36+6 wk)
    - A: number of abortions (loss of intrauterine pregnancy prior to viability of fetus <20 wk or <500 g fetal weight)
      - induced (therapeutic) and spontaneous (miscarriage)
    - L: number of living children
- symptoms: amenorrhea, N/V, breast tenderness, urinary frequency, fatigue

Physical Signs
- Goodell's sign: softening of the cervix (4-6 wk)
- Chadwick's sign: bluish discoloration of the cervix and vagina due to pelvic vasculature engorgement (6 wk)
- Hegar's sign: softening of the cervical isthmus (6-8 wk)
- uterine enlargement
- breast engorgement

Acronyms
- AC abdominal circumference
- ACOG American Congress of Obstetricians and Gynecologists
- AFI amniotic fluid index
- AFLP acute fatty liver of pregnancy
- AFV amniotic fluid volume
- AP anteroposterior
- APS antiphospholipid antibody syndrome
- BPP biophysical profile
- C/S Cesarean section
- CDH cephalic disproportion
- CGD chorionic villus sampling
- DIC disseminated intravascular coagulation
- DVT deep vein thrombosis
- ECV external cephalic version
- EDD estimated date of delivery
- EDF estimated fetal weight
- FDP fibrin degradation products
- FHR fetal heart rate
- FISH fluorescence in situ hybridization
- FL femur length
- FM fetal movement
- FPG fasting plasma glucose
- FSH follicle stimulating hormone
- FTS first trimester screen
- GA gestational age
- GBS Group B Streptococcus
- GDM gestational diabetes mellitus
- GTN gestational trophoblastic neoplasia
- HC head circumference
- HELLP hemolysis, elevated liver enzymes, low platelets
- IGF infant growth factors
- IIM intramyometrial
- IDL induction of labor
- IPS integrated prenatal screen
- IUFD intrauterine fetal death
- IUGR intrauterine growth restriction
- IVP intravenous pyelogram
- IVD intraventricular hemorrhage
- LLP left lateral decubitus position
- LMP last menstrual period
- MSAM maternal serum a-fetoprotein
- MSAF maternal serum screen
- MTX methotrexate
- NTDs neural tube defects
- NTUS nuchal translucency ultrasound
- OA occiput anterior
- OGT open oral glucose tolerance test
- OTT open neural tube defect
- OP occiput posterior
- OTT open oral tolerance test
- PPAP pregnancy-associated plasma protein a
- PPD postpartum depression
- PPFT postpartum hemorrhage
- PROM preterm premature rupture of membranes
- VRM premature rupture of membranes
- PTL preterm labor
- RDGS respiratory distress syndrome
- ROM rupture of membranes
- SA spontaneous abortion
- SFH symphysis fundal height
- SVD spontaneous vaginal delivery
- TENS transcutaneous electrical nerve stimulation
- TPN total parenteral nutrition
- UTR urinary tract infection
- VBAC vaginal birth after Cesarean

Figure 1. Placental blood flow

- Umbilical arteries (deoxygenated blood)
- Umbilical vein (oxygenated blood)
- Placenta
- • site of fetal nutritive, respiratory, and excretory function
- • discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by fissures into cotyledons (lobules) on the uterine side
- • produces hormones such as progesterone, placental lactogen, estrogen, relaxin, β-hCG, and IGFs
- • poor implantation can lead to spontaneous abortion
- • abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see Antepartum Hemorrhage, OB24)
Investigations
- **β-hCG**: peptide hormone composed of α and β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy
  - positive in serum 9 d post-conception, positive in urine 28 d after first day of LMP
  - plasma levels double every 1-2 d, peak at 8-10 wk, then fall to a plateau until delivery
  - levels less than expected by dates suggest: ectopic pregnancy, abortion, or inaccurate dates
  - levels higher than expected suggest: multiple gestation, molar pregnancy, Trisomy 21, or inaccurate dates
- **U/S**
  - transvaginal
    - 5 wk: gestational sac visible
    - 6 wk: fetal pole seen
    - 7-8 wk: fetal heart tones visible
  - transabdominal
    - 6-8 wk: intrauterine pregnancy visible (β-hCG ≥6,500 mIU/mL)

Maternal Physiology

<table>
<thead>
<tr>
<th>Table 1. Physiologic Changes During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Skin</strong></td>
</tr>
<tr>
<td>Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation) Other: spider angiomas, palmar erythema due to increased estrogen, striae gravidarum due to connective tissue changes</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
</tr>
<tr>
<td>Hyperdynamic circulation</td>
</tr>
<tr>
<td>Increased CO, HR, and blood volume</td>
</tr>
<tr>
<td>Decreased BP due to decreased PVR</td>
</tr>
<tr>
<td>Enlarging uterus compresses IVC and pelvic veins</td>
</tr>
<tr>
<td>Decreased venous return leads to risk of hypotension</td>
</tr>
<tr>
<td>Increased venous pressure leads to risk of varicose veins, hemorrhoids, leg edema</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
</tr>
<tr>
<td>Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit</td>
</tr>
<tr>
<td>Increased leukocyte count but impaired function leads to improvement in autoimmune diseases</td>
</tr>
<tr>
<td>Gestational thrombocytopenia: mild (platelets &gt;70,000/µL) and asymptomatic, normalizes within 2-12 wk following delivery</td>
</tr>
<tr>
<td>Hypercoagulable state: increased risk of DVT and PE but also decreased bleeding at delivery</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
</tr>
<tr>
<td>Increased incidence of nasal congestion and epistaxis</td>
</tr>
<tr>
<td>Increased O₂ consumption to meet increased metabolic requirements</td>
</tr>
<tr>
<td>Elevated diaphragm (i.e. patient appears more “barrel-chested”)</td>
</tr>
<tr>
<td>Increased minute ventilation leads to decreased CO₂ resulting in mild respiratory alkalosis that helps CO₂ diffuse across the placenta from fetal to maternal circulation</td>
</tr>
<tr>
<td>No change in VC and FEV₁</td>
</tr>
<tr>
<td>Decreased TLC, FRC, and RV</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
</tr>
<tr>
<td>GERD due to increased intra-abdominal pressure and progesterone (causing decreased sphincter tone and delayed gastric emptying)</td>
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<tr>
<td>Increased gallstones due to progesterone causing increased gallbladder stasis</td>
</tr>
<tr>
<td>Constipation and hemorrhoids due to progesterone causing decreased GI motility</td>
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<tr>
<td><strong>Genitourinary</strong></td>
</tr>
<tr>
<td>Increased urinary frequency due to increased total urinary output</td>
</tr>
<tr>
<td>Increased incidence of UTI and pyelonephritis due to urinary stasis (see Urinary Tract Infection, OB19)</td>
</tr>
<tr>
<td>Glycosuria that can be physiologic especially in the 3rd trimester</td>
</tr>
<tr>
<td>Ureters and renal pelvis dilation (R&gt;L) due to progesterone-induced smooth muscle relaxation and uterine enlargement</td>
</tr>
<tr>
<td>Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 0.4-0.5 mg/dL), uric acid, and BUN</td>
</tr>
<tr>
<td><strong>Neurologic</strong></td>
</tr>
<tr>
<td>Increased incidence of carpal tunnel syndrome and Bell’s palsy</td>
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<tr>
<td><strong>Endocrine</strong></td>
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<tr>
<td>Thyroid: moderate enlargement and increased basal metabolic rate</td>
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<tr>
<td>Increased total thyroxine and thyroxine binding globulin (TBG)</td>
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<tr>
<td>Free thyroxine index and TSH levels are normal</td>
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<tr>
<td>Adrenal: maternal cortisol rises throughout pregnancy (total and free)</td>
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<tr>
<td>Calcium: decreased total maternal Ca²⁺ due to decreased albumin</td>
</tr>
<tr>
<td>Free ionized Ca²⁺ (i.e. active) proportion remains the same due to parathyroid hormone (PTH), results in increased bone resorption and gut absorption, increased bone turnover (but no loss of bone density due to estrogen inhibition)</td>
</tr>
</tbody>
</table>
Prenatal Care

- provided by obstetrician, family doctor, midwife, or multidisciplinary team (based on patient preference and risk factors)
- Antenatal Records (province specific)

Preconception Counseling

- 3-8 wk GA is a critical period of organogenesis, so early preparation is vital
- past medical history: optimize medical illnesses and necessary medications prior to pregnancy (see Medical Conditions in Pregnancy, OB13, and Medications in Pregnancy, OB10)

supplementation
- folic acid: encourage diet rich in folic acid and supplement 8-12 wk preconception until end of T1 to prevent NTDs
  - 0.4-1 mg daily in all women; 5 mg if previous NTD, antiepileptic medications, DM, or BMI >35 kg/m²
- iron supplementation, prenatal vitamins

risk modification
- lifestyle: balanced nutrition and physical fitness
- medications: patients with chronic diseases should discuss whether their medications may be teratogenic prior to conception so they may be adjusted; it is not advised to stop medications abruptly when becoming pregnant
- infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV
- genetic testing as appropriate for high risk groups (see Prenatal Screening, Table 2); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay or birth anomalies
- social: alcohol, smoking, drug use, domestic violence (see Family Medicine, FM12, FM10, FM28)

Initial Prenatal Visit

- usually within 12 wk of the first day of LMP or earlier if <20 or >35 yr old or other risk factors are present
- Antenatal Records are filled out on the first prenatal visit

History
- gestational age by dates from the first day of the LMP
- if LMP unreliable, get a dating ultrasound which could coincide with nuchal translucency at ~12 wks
- dates should change if T1 U/S is greater than 5 days in difference from LMP due date
  - 1st day of LMP + 7 d – 3 mo
  - e.g. LMP = 1 Apr 2013, EDC = 8 Jan 2014 (modify if cycle >28 d by adding number of d >28)
- history of present pregnancy (e.g. bleeding, N/V)
- history of all previous pregnancies
- past medical history, past gynecological history
- prescription and non-prescription medications
- family history: genetic disease, birth defects, multiple gestation
- social history: smoking, alcohol, drug use, domestic violence (see Family Medicine, FM10, FM12, FM28), consanguinity

Physical Exam
- complete exam to obtain baseline patient information
- BP and weight important for interpreting subsequent changes
- pelvic exam

Investigations
- blood work
  - CBC, blood group and type, Rh antibodies, infection screening as per preconception counseling
- urine R&E, C&S
- screen for bacteriuria and proteinuria
- pelvic exam
  - Pap smear (only if required according to patient history and state screening guidelines), cervical culture for N. gonorrhoeae (GC) and C. trachomatis, vaginal swab for bacterial vaginosis (BV)

Prenatal and genetic screening are voluntary and require proper counseling and informed consent before proceeding. HIV is done automatically in some states as opt-out testing, need to inform patient.
Subsequent Prenatal Visits

Timing
- for uncomplicated pregnancies, q4-6wk until 28 wk, q2-3wk from 28 to 36 wk, and weekly from 36 wk until delivery

Assess at Every Visit
- record estimated GA
- history of present pregnancy: fetal movements, uterine bleeding, leaking, cramping
- physical exam: BP, weight gain, thyroid exam, SFH, Leopold's maneuvers (T3) for lie, position, and presentation of fetus
- investigations: urinalysis for glucosuria, proteinuria; fetal heart rate starting at 12 wk using Doppler U/S

Leopold's Maneuvers
- performed after 30-32 wk gestation
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver: to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

Screening Tests
- testing should only occur following counseling and with the informed consent from the patient

<table>
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<tr>
<th>Disease (Inheritance)</th>
<th>Population(s) at Risk</th>
<th>Screening Test(s)</th>
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<tbody>
<tr>
<td>Thalassemia (AR)</td>
<td>Mediterranean, South East Asian, Western Pacific, African, Middle Eastern, Caribbean, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis, or HPLC</td>
</tr>
<tr>
<td>Sickle Cell (AR)</td>
<td>African, Caribbean, Mediterranean, Middle Eastern, Indian, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis, or HPLC</td>
</tr>
<tr>
<td>Cystic Fibrosis (CF) (AR)</td>
<td>Mediterranean, Finnish, Caucasian, or FHx</td>
<td>CFTR gene DNA analysis</td>
</tr>
<tr>
<td>Tay Sachs Disease (AR)</td>
<td>Ashkenazi Jewish*, French Canadians, Cajun</td>
<td>Enzyme assay HEXA, or DNA analysis HEXA gene</td>
</tr>
<tr>
<td>Fragile X Syndrome (X-linked)</td>
<td>Family history – confirmed or suspected</td>
<td>DNA analysis: FMR-1 gene</td>
</tr>
</tbody>
</table>

AR = autosomal recessive; HEXA = hexosaminidase A; HPLC = high performance liquid chromatography
*If both partners are Ashkenazi Jewish, test for Caravan disease and Familial Dysautonomia (FD); if family history of a specific condition, look for carrier status: e.g. Gaucher, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners positive, refer for genetic counseling

Small for Dates
- Date miscalculation
- IUGR
- Fetal demise
- Oligohydramnios

Large for Dates
- Date miscalculation
- Multiple gestation
- Polyhydramnios
- LGA (familial, DM)
- Fibroids
Table 3. Gestation-Dependent Screening Investigations

<table>
<thead>
<tr>
<th>Gestational Age (wk)</th>
<th>Investigations</th>
<th>Details</th>
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</thead>
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<tr>
<td>8-12</td>
<td>Dating U/S, possible Pap smear, chlamydia/gonorrhea cultures, urine C/S, HIV, VDRL, HepBAg, Rubella IgG, Parvovirus IgM or IgG if high risk (small child at home or daycare worker/primary teacher), Varicella IgG if no history of disease/immunization, CBC, blood group and screen</td>
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<tr>
<td>10-12</td>
<td>CVS</td>
<td>Measures</td>
</tr>
<tr>
<td>11-14</td>
<td>FTS, IPS Part 1</td>
<td>1. Nuchal translucency on U/S</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. β-hCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. PAPP-A</td>
</tr>
<tr>
<td>11-14</td>
<td>Nuchal translucency U/S</td>
<td></td>
</tr>
<tr>
<td>15-16 to term</td>
<td>Amniocentesis</td>
<td>Measures</td>
</tr>
<tr>
<td>15-20</td>
<td>IPS Part 2</td>
<td>1. MSAFP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. β-hCG</td>
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<tr>
<td></td>
<td></td>
<td>3. Unconjugated estrogen (estriol or µE3)</td>
</tr>
<tr>
<td>15-20</td>
<td>MSS (or MSAFP only for patients who did FTS earlier)</td>
<td>Measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. MSAFP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. β-hCG</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Unconjugated estrogen (estriol or µE3)</td>
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<tr>
<td>18-20 to term</td>
<td>Fetal movements (quickening)</td>
<td></td>
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<tr>
<td>18-20</td>
<td>U/S for dates, fetal growth, and anatomy assessment</td>
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<tr>
<td>24-28</td>
<td>50 g OGCT</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Repeat CBC</td>
<td>RhIG for all Rh negative women</td>
</tr>
<tr>
<td>35-37</td>
<td>GBS screen</td>
<td></td>
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<tr>
<td>6 wk postpartum</td>
<td>Discuss contraception, menses, breastfeeding, depression, mental health, support</td>
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<td></td>
<td>Physical exam: breast exam, pelvic exam including Pap smear</td>
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</tbody>
</table>

Maternal serum screen is also referred to as Triple Screen; if Inhibin A is also tested, it is referred to as Quadruple Screen
Ideally testing for MSS and IPS Part 2 occur between 15-18 wk to give women more time to make decisions and move ahead with diagnostic testing should the resulting screen be positive

Ultrasound Screening
- dating ultrasound best done between 8-12 wk GA (most accurate form of pregnancy dating)
  - measurement of crown-rump length (margin of error ± 5 d)
  - change EDC to U/S date if >5 d discrepancy from EDC based on LMP
- NTUS at 11-14 wk GA
  - measures the amount of fluid behind the neck of the fetus
  - early screen for Trisomy 21 (may also detect cardiac and other aneuploidies like Turner’s syndrome)
  - NT measurement is necessary for the FTS and IPS Part 1
- fetal growth and anatomy ultrasound routinely done at 18-20 wk GA (margin of error ± 10 d)
- earlier or subsequent ultrasounds performed when medically indicated

Table 4. Comparison of FTS, MSS, and IPS

<table>
<thead>
<tr>
<th></th>
<th>FTS 11-14 wk</th>
<th>MSS 15-20 wk</th>
<th>IPS 15-20 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk estimate for</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Down syndrome (Trisomy 21): increased NT, increased β-hCG, decreased PAPP-A</td>
<td>Risk estimate for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. oNTD: increased MSAFP (sensitivity 80-90%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Trisomy 21: decreased MSAFP, increased β-hCG, decreased µE3 (sensitivity 65%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Trisomy 18: decreased MSAFP, decreased β-hCG, decreased µE3 (sensitivity 80%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: does not measure risk of open neural tube defect (oNTD) and should be combined with MSAFP at 16 wk
Useful where patient wants results within the first trimester
More accurate estimate of Down syndrome risk than MSS, sensitivity ~85% (when combined with age)
5% false positive rate
Patients with positive screen should be offered CVS, amniocentesis, or NIPT (covered in some provinces, self-pay in others)

Risk estimate for oNTD, Trisomy 21, Trisomy 18
Sensitivity ~85-90%
2% false positive rate
Patients with positive screen should be offered U/S and/or amniocentesis or NIPT

Note: In twins, FTS, MSS, and IPS are not applicable; screen with NT for chromosomal abnormalities and MSAFP for oNTDs
Diagnostic Tests

Indications
- maternal age >35 yr (increased risk of chromosomal anomalies)
- risk factors in current pregnancy
  - abnormal U/S
  - abnormal prenatal screen (IPS, FTS, or MSS)
- past history/family history of:
  - previous pregnancy with chromosomal anomaly or genetic disease
  - either parent a known carrier of a genetic disorder or balanced translocation
  - family history of chromosomal anomaly, genetic disorder, birth defect, or undiagnosed mental retardation
  - consanguinity
  - three or more spontaneous abortions

AMNIOCENTESIS
- U/S-guided transabdominal extraction of amniotic fluid

Indications
- identification of genetic anomalies (15-16 wk gestation) as per indications above
- assessment of fetal lung maturity (T3) via the L/S ratio (lecithin:sphingomyelin)
  - if >2:1, RDS is less likely to occur

Advantages
- also screens for oNTD (acetylcholinesterase and amniotic AFP) – 96% accurate
- in women >35 yr, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- more accurate genetic testing than CVS

Disadvantages
- 1/400 – 1/500 risk of spontaneous abortion
- results take 14-28 d; FISH can be done on chromosomes X, Y, 21, 13, 18 to give preliminary results in 48 h

CHORIONIC VILLUS SAMPLING
- biopsy of fetal-derived chorion using a transabdominal needle or transcervical catheter at 10-12 wk

Advantages
- enables pregnancy to be terminated earlier than with amniocentesis
- rapid karyotyping and biochemical assay within 48 h, including FISH analysis
- high sensitivity and specificity

Disadvantages
- 1-2% risk of spontaneous abortion
- does not screen for oNTD
- 1-2% incidence of genetic mosaicism “false negative” results

ISOIMMUNIZATION SCREENING

Definition
- isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigenic stimulation with RBC of another individual

Etiology
- maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
- in pregnancy, anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
- overall risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16%
- sensitization routes
  - incompatible blood transfusions
  - previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy, abruption)
  - invasive procedures in pregnancy (e.g. prenatal diagnosis, cerclage, D&C)
  - any type of abortion
  - labor and delivery

NON-INVASIVE PRENATAL TESTING (NIPT)
- New non-invasive screening for Down syndrome in spontaneous singleton pregnancies
- Analyzes maternal blood for circulating cell free fetal DNA (ccffDNA) at 10 wk GA
- High sensitivity (98-99%), FP<2%
- Disadvantages: less sensitive for Trisomy 18 and 13, does not screen for oNTD, not widely available

DDx of Increased MSAFP
- Incorrect GA
- >1 fetus (e.g. twins)
- Fetal demise
- oNTD
- Abdominal wall defects (e.g. omphalocele)

DDx of Decreased MSAFP
- Incorrect GA
- Gestational trophoblastic neoplasia
- Missed abortion
- Chromosomal anomalies
- Maternal diabetes

Compared to CVS, amniocentesis has a higher accuracy of prenatal cytogenetic diagnosis (99.8% vs. 97.5%) and lower risk of spontaneous abortion (0.5% vs. 1-2%)

Risk Factors for Neural Tube Defects

GRIMM
- Genetics: family history of NTD (risk of having second child with NTD is increased to 2-5%), consanguinity, chromosomal (characteristic of Trisomy 13, 18, and 21)
- Race: European Caucasians > African Americans, 3-fold higher in Hispanics
- Insufficient vitamins: zinc and folate
- Maternal chronic disease (e.g. DM)
- Maternal use of antiepileptic drugs

General population risk for NTD is 0.1%
Investigations
- routine screening with indirect Coombs test at first visit for blood group, Rh status, and antibodies
- Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage by estimating volume of fetal blood volume that entered maternal circulation
- detailed U/S for hydrops fetalis

Prophylaxis
- exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
- Rhogam® (300 µg) given to all Rh negative and antibody screen negative women in the following scenarios
  - routinely at 28 wk GA (provides protection for ~12 wk)
  - within 72 h of the birth of an Rh positive fetus
  - with a positive Kleihauer-Betke test
  - with any invasive procedure in pregnancy (CVS, amniocentesis)
  - in ectopic pregnancy
  - with miscarriage or therapeutic abortion (only 50 µg required)
  - with an antepartum hemorrhage
- if Rh negative and Ab screen positive, follow mother with serial monthly Ab titles throughout pregnancy ± serial amniocentesis as needed (Rhogam® has no benefit)

Investigations
- MCA dopplers are done to assess degree of fetal anemia or if not available bilirubin is measured by serial amnioctenesis to assess the severity of hemolysis
- cordocentesis for fetal Hb should be used cautiously (not first line)

Treatment
- falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
- intrauterine transfusion of O-negative pRBCs may be required for severely affected fetus or early delivery of the fetus for exchange transfusion

Complications
- anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, ascites
- severe cases can lead to fetal hydrops (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)

GROUP B STREPTOCOCCUS SCREEN

Epidemiology
- 15-40% vaginal carrier rate

Risk Factors (for neonatal disease)
- GBS bacteriuria during current pregnancy even if treated
- previous infant with invasive GBS infection
- preterm labor <37 wk
- ruptured membranes >18 h before delivery
- intrapartum maternal temperature 100.4°F
- positive GBS screen during current pregnancy

Clinical Features
- not harmful to mother
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia, and death)

Investigations
- offer screening to all women at 35-37 wk with vaginal and anorectal swabs for C&S

Treatment
- treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
- indications for antibiotic prophylaxis: positive GBS screen or GBS status unknown and one of the risk factors
- antibiotics for GBS prophylaxis
  - penicillin G 5 million units IV then 2.5 million units IV q4h until delivery
  - penicillin allergic but not at risk for anaphylaxis: cefazolin 2 g IV then 1 g q8h
  - penicillin allergic and at risk for anaphylaxis: vancomycin 1 g IV q12h until delivery
- if fever, broad spectrum antibiotic coverage is advised
Counseling of the Pregnant Woman

Nutrition

- 3-4 servings of milk products daily (greater if multiple gestation)
- a daily caloric increase of ~100 cal/d in the first trimester, ~300 cal/d in the second and third trimesters and ~450 cal/d during lactation
- daily multivitamin should be continued in the second trimester for women who do not consume an adequate diet; otherwise routine vitamin supplementation is not necessary (avoid excess vitamin A)
- nutrients important during pregnancy
  - folic acid: 0.4 mg/d for first 12 wk (5 mg/d if high risk)
    - supports maternal increase in blood volume, growth of maternal and fetal tissue, decreases incidence of neural tube defects
    - foods rich in folic acid include: spinach, lentils, chick peas, asparagus, broccoli, peas, Brussels sprouts, corn, and oranges
  - calcium: 1,200-1,500 mg/d
    - maintains integrity of maternal bones, skeletal development of fetus, breast milk production
  - vitamin D: 1,000 IU
    - promotes calcium absorption
  - iron: 0.8 mg/d in T1, 4-5 mg/d in T2, and >6 mg/d in T3
    - supports maternal increase in blood cell mass, supports fetal and placental tissue
    - required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
    - iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see Iron Deficiency Anemia, OB13)
  - essential fatty acids – supports fetal neural and visual development
    - contained in vegetable oils, margarines, peanuts, fatty fish

Caffeine

- diuretic and stimulant that readily crosses placenta
- less than 300 mg/d is not thought to contribute to miscarriage or preterm birth (ACOG)
- relationship between caffeine and IUGR is unknown (ACOG)
- 1-2 cups/d is accepted as safe during pregnancy

Herbal Teas and Preparations

- not enough scientific information about safety of various herbs and herbal products to recommend their use during pregnancy
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- chamomiles have been reported to exhibit adverse effects on the uterus

Food Borne Illnesses

- microbiological contamination of food may occur through cross-contamination and/or improper food handling
  - listeriosis (Listeria monocytogenes) and toxoplasmosis (Toxoplasma gondii) are of concern during pregnancy
  - avoid consumption of raw meats, fish, poultry, raw eggs, and unpasteurized dairy products
  - avoid unpasturized soft cheeses, deli meats, smoked salmon, and pates as they may be sources of Listeria
- chemical contamination of food
  - current guideline for mercury of 0.5 ppm in fish is not considered harmful for the general population, including pregnant women
  - consumption of top predator fish such as shark, swordfish, king mackerel, tilefish, and fresh/frozen tuna (not canned tuna) should be limited to one meal per month

Lifestyle

- exercise under physician guidance
- absolute contraindications
  - ruptured membranes, preterm labor, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestations (>3), placenta previa after 28th wk, persistent 2nd or 3rd trimester bleeding, uncontrolled type 1 DM, uncontrolled thyroid disease, or other serious cardiovascular, respiratory, or systemic disorder
• relative contraindications
  ▪ previous preterm birth, mild/moderate cardiovascular or respiratory disorder, anemia (Hb ≤10 g/dL), malnutrition or eating disorder, twin pregnancy after 28th wk, other significant medical conditions
• weight gain: optimal gain depends on pre-pregnancy BMI (varies from 6.8–18.2 kg)
• work: strenuous work, extended hours and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
• travel: not harmful, but stress related to travel may be associated with preterm labor
  ▪ air travel is acceptable in second trimester; airline cutoff for travel is 36–38 wk gestation depending on the airline to avoid giving birth on the plane
• sexual intercourse: may continue, except in patients at risk for: abortion, preterm labor, or placenta previa; breast stimulation may induce uterine activity and is discouraged in high-risk patients near term
• smoking: assist/encourage to reduce or quit smoking
  ▪ increased risk of: decreased birth weight, placenta previa/abruption, spontaneous abortion, preterm labor, stillbirth
• alcohol: no amount of alcohol is safe in pregnancy; encourage abstinence from alcohol during pregnancy; alcohol increases incidence of abortion, stillbirth, and congenital anomalies
  ▪ fetal alcohol syndrome (see Pediatrics, P24)
• cocaine: microcephaly, growth retardation, prematurity, abruptio placentae

Medications

• most drugs cross the placenta to some extent
• very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
• use any drug with caution and only if necessary
• analgesics: acetaminophen preferable to ASA or ibuprofen

Table 5. Documented Adverse Effects, Contraindicated

<table>
<thead>
<tr>
<th>Contraindicated Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Fetal renal defects, IUGR, oligohydramnios</td>
</tr>
<tr>
<td>tetracycline</td>
<td>Stains infant’s teeth, may affect long bone development</td>
</tr>
<tr>
<td>retinoids (e.g. Accutane®)</td>
<td>CNS, craniofacial, cardiac, and thymic anomalies</td>
</tr>
<tr>
<td>DES (and other estrogenic or androgenic compounds)</td>
<td>Vaginal adenosis, adenocarcinoma, uterine malformation in females exposed to DES in utero</td>
</tr>
<tr>
<td>misoprostol</td>
<td>Mobius syndrome (congenital facial paralysis with or without limb defects, spontaneous abortion, preterm labor)</td>
</tr>
</tbody>
</table>

Table 6. Documented Adverse Effects, Weigh Benefits vs. Risks, and Consider Medication Change

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenytoin</td>
<td>Fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmophogenesis, congenital anomalies)</td>
</tr>
<tr>
<td>valproate</td>
<td>oNTD in 1%</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>oNTD in 1-2%</td>
</tr>
<tr>
<td>lithium</td>
<td>Ebstein’s cardiac anomaly, goiter, hypotriatremia</td>
</tr>
<tr>
<td>warfarin</td>
<td>Increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR, fetal warfarin syndrome (nasal hypoplasia, epiphyseal stippling, optic atrophy, mental retardation, intracranial hemorrhage)</td>
</tr>
<tr>
<td>erythromycin</td>
<td>Maternal liver damage (acute fatty liver)</td>
</tr>
<tr>
<td>sulpha drugs</td>
<td>Anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3</td>
</tr>
<tr>
<td>chloramphenicol</td>
<td>Gray baby syndrome (fetal circulatory collapse 2° to toxic accumulation)</td>
</tr>
</tbody>
</table>

Immunizations

Intrapartum

• administration is dependent on the risk of infection vs. risk of immunization complications
• safe: tetanus toxoid, diphtheria, influenza, hepatitis B, pertussis
• avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, varicella
• contraindicated: rubella, oral typhoid

Postpartum

• rubella vaccine for all non-immune mothers
• hepatitis B vaccine should be given to infant within 12 h of birth if maternal status unknown or positive – follow-up doses at 1 and 6 mo
• human papillomavirus (HPV) vaccine – if meets criteria
• safe: tetanus toxoid, diphtheria, influenza, hepatitis B, pertussis
Radiation

- ionizing radiation exposure is considered teratogenic at high doses
  - if indicated for maternal health, should be done
- imaging not involving direct abdominal/pelvic high dosage is not associated with adverse effects
  - higher dosage to fetus: plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen, pelvis, lumbar spine
- most investigations involve minimal radiation exposure
- radioactive isotopes of iodine are contraindicated
- no known adverse effects from U/S or MRI (long-term effects of gadolinium unknown, avoid if possible)

### Table 7. Approximate Fetal Doses from Common Diagnostic Procedures

<table>
<thead>
<tr>
<th>Examination</th>
<th>Estimated Fetal Dose (rad)</th>
<th>Number of Exams Safe in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plain Film</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0-14</td>
<td>35</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0-11</td>
<td>45</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0-17</td>
<td>29</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>0.009</td>
<td>555</td>
</tr>
<tr>
<td>Chest (2 views)</td>
<td>&lt;0.001</td>
<td>5,000</td>
</tr>
<tr>
<td><strong>CT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0-8</td>
<td>6</td>
</tr>
<tr>
<td>Pelvis</td>
<td>2-5</td>
<td>2</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0-24</td>
<td>20</td>
</tr>
<tr>
<td>Chest</td>
<td>0.006</td>
<td>833</td>
</tr>
</tbody>
</table>


Termination of Pregnancy

- see Gynecology, GY20

### Definition

- active termination of a pregnancy before fetal viability (usually <500 g or <20 wk GA)

### Indications

- inability to carry a pregnancy to term due to medical or social reasons (including patient preference)

### Management

- medical
  - <9 wk: methotrexate + misoprostol
  - >12 wk: prostaglandins (intra- or extra-amniotically or IM) or misoprostol
- surgical
  - <12 wk: dilatation + vacuum aspiration + curettage
  - >12 wk: dilatation and evacuation, early induction of labor
  - common complications: pain or discomfort
  - less common complications: hemorrhage, perforation of uterus, laceration of cervix, risk of infertility, infection/endometritis, Asherman’s syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), retained products of conception
- counseling
  - supportive and counseling services
  - future contraception and family planning services
  - ensure follow-up

CMA Policy (1988)

“Induced abortion should be uniformly available to all women in Canada”
and “there should be no delay in the provision of abortion services”

Terminations are generally done until the stage of viability (~23.5 wk), although this varies depending on the provider

For prevention of pregnancy after rape, ensure appropriate access to emergency contraception (see Gynecology, GY20)
Prenatal Fetal Monitoring

Fetal Movements

- Patients will generally first notice fetal movement ("quickening") at 18-20 wk in primigravidas; can occur 1-2 wk earlier in multigravidas; can occur 1-2 wk later if placenta is implanted on the anterior wall of uterus.
- If the patient is concerned about decreased fetal movement, she is counseled to choose a time when the fetus is normally active to count movements (usually recommended after 26 wk).
- All high risk women should be told to do FM counts.
  - If there is a subjective decrease in fetal movement, try drinking juice, eating, changing position, or moving to a quiet room and count for 2 h; ≥6 movements in 2 h expected.
  - If there are <6 movement counts in 2 h, patient should present to labor and delivery triage.

Non-Stress Test

Definition

- FHR tracing ≥20 min using an external Doppler to assess FHR and its relationship to fetal movement (see Fetal Monitoring in Labor, OB33).

Indication

- Any suggestion of uteroplacental insufficiency or suspected compromise in fetal well-being.

Table 8. Classification of Antepartum Non-Stress Test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal NST (Previously &quot;Reactive&quot;)</th>
<th>Atypical NST (Previously &quot;Non-Reactive&quot;)</th>
<th>Abnormal NST (Previously &quot;Non-Reactive&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>110-160 bpm</td>
<td>100-110 bpm or &gt;160 bpm for &lt;30 min Rising baseline</td>
<td>Bradycardia &lt;100 bpm Tachycardia &gt;160 for &gt;30 min Erratic baseline</td>
</tr>
<tr>
<td>Variability</td>
<td>6-25 bpm (moderate) ≤5 (absent or minimal) for &lt;40 min</td>
<td>5 (absent or minimal) for 40-80 min</td>
<td>≤5 for 80 min Sinusoidal 25 bpm for &gt;10 min</td>
</tr>
<tr>
<td>Decelerations</td>
<td>None or occasional variable &lt;30 s</td>
<td>Variable decelerations 30-60 s duration</td>
<td>Variable decelerations &gt;60 s Late deceleration(s)</td>
</tr>
<tr>
<td>Accelerations in Term Fetus</td>
<td>2 accelerations with acme of ≥15 bpm, lasting 15 s over &lt;40 min of testing</td>
<td>2 accelerations with acme of ≥15 bpm, lasting 15 s in 40-80 min</td>
<td>&lt;2 accelerations with acme of ≥15 bpm, lasting 15 s in &gt;80 min</td>
</tr>
<tr>
<td>Accelerations in Preterm Fetus (&lt;32 wk)</td>
<td>&gt;2 accelerations with acme of &gt;10 bpm, lasting 10 s in &lt;40 min</td>
<td>&lt;2 accelerations with acme of &gt;10 bpm, lasting 10 s in 40-80 min</td>
<td>&lt;2 accelerations with acme of &gt;10 bpm, lasting 10 s in &gt;80 min</td>
</tr>
<tr>
<td>Action</td>
<td>FURTHER ASSESSMENT OPTIONAL, based on total clinical picture</td>
<td>FURTHER ASSESSMENT REQUIRED</td>
<td>URGENT ACTION REQUIRED An overall assessment of the situation and further investigation with U/S or BPP is required; some situations will require delivery</td>
</tr>
</tbody>
</table>

Operating Characteristics

- False positive rate depends on duration; false negative rate = 0.2-0.3%.

Interpretation

- Normal: at least 2 accelerations of FHR >15 bpm from the baseline lasting >15 s, in 20 min.
- Abnormal: <2 accelerations of FHR in 40 min.
- If no observed accelerations or fetal movement in the first 20 min, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 min.
- If NST abnormal, then perform BPP.

Biophysical Profile

Definition

- U/S assessment of the fetus ± NST.

Indications

- Abnormal or atypical NST.
- Post-term pregnancy.
- Decreased fetal movement.
- Any other suggestion of fetal distress or uteroplacental insufficiency.

DDx of Decreased Fetal Movements

- DASH
- Death of fetus
- Amniotic fluid decreased
- Sleep cycle of fetus
- Hunger/Thirst
Operating Characteristics

- False positive rate ≤30%, false negative rate = 0.1%

Table 9. Scoring of the BPP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reassuring (2 points)</th>
<th>Non-Reassuring (0 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFV*</td>
<td>Fluid pocket of 2 cm in 2 axes</td>
<td>Oligohydramnios</td>
</tr>
<tr>
<td>Breathing</td>
<td>At least one episode of breathing lasting at least 30 s</td>
<td>No breathing</td>
</tr>
<tr>
<td>Limb Movement</td>
<td>Three discrete movements</td>
<td>Two or less</td>
</tr>
<tr>
<td>Fetal Tone</td>
<td>At least one episode of limb extension followed by flexion</td>
<td>No movement</td>
</tr>
</tbody>
</table>

*AFV* is a marker of chronic hypoxia, all other parameters indicate acute hypoxia

Interpretation

- 8: perinatal mortality rate 1:1,000; repeat BPP as clinically indicated
- 6: perinatal mortality 31:1,000; repeat BPP in 24 h
- 0-4: perinatal mortality rate 200:1,000; deliver fetus if benefits of delivery outweigh risks

Medical Conditions in Pregnancy

Iron and Folate Deficiency Anemia

Table 10. Iron Deficiency and Folate Deficiency Anemia

<table>
<thead>
<tr>
<th>Iron Deficiency Anemia</th>
<th>Folate Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>See Hematology H15</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Responsible for 80% of causes of non-physiologic anemia during pregnancy</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>See Hematology, H15</td>
</tr>
<tr>
<td>Investigations</td>
<td>See Hematology, H15</td>
</tr>
<tr>
<td>Management</td>
<td>Prevention (non-anemic): 30 mg elemental iron/d (met by most prenatal vitamins)</td>
</tr>
<tr>
<td></td>
<td>Treatment (anemic): 30-120 mg elemental iron/d</td>
</tr>
<tr>
<td></td>
<td>325 mg ferrous fumarate = 106 mg elemental Fe^{2+}; 325 mg ferrous sulfate = 65 mg elemental Fe^{2+}; 325 mg ferrous gluconate = 38 mg elemental Fe^{2+}; Polysaccharide-Iron Complex = 150 mg elemental Fe^2+ capsule</td>
</tr>
<tr>
<td>Complications</td>
<td>Maternal: angina, CHF, infection, slower recuperation, preterm labor</td>
</tr>
<tr>
<td></td>
<td>Fetal: decreased oxygen carrying capacity leading to fetal distress, IUGR, and low birth weight</td>
</tr>
<tr>
<td>Notes</td>
<td>Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake</td>
</tr>
<tr>
<td></td>
<td>Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg), and losses (200 mg) – more needed for multiple gestations</td>
</tr>
<tr>
<td></td>
<td>Folic acid is necessary for closure of neural tube during early fetal development (by day 28 of gestation)</td>
</tr>
</tbody>
</table>

Diabetes Mellitus

Classification of Diabetes Mellitus

- Type 1 and type 2 DM (see Endocrinology, E6)
- GDM: onset of DM during pregnancy

Etiology

- Type 1 and type 2 DM
- GDM: usually around 24-28 wk GA, anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → higher fasting glucose → leading to GDM and/or exacerbating pre-existing DM

Epidemiology

- 2-4% of pregnancies are complicated by DM
MANAGEMENT

A. TYPE 1 AND TYPE 2 DM

Preconception
- pre-plan and refer to high-risk clinic
- optimize glycemic control
- counsel patient re: potential risks and complications
- evaluate for diabetic retinopathy, neuropathy, CAD

Pregnancy
- if already on oral medication, generally switch to insulin therapy
  - continuing glyburide or metformin controversial
  - teratogenicity unknown for other oral anti-hyperglycemics
- tight glycemic control
  - insulin dosage may need to be adjusted in type 2 due to increased demand and increased insulin resistance
- monitor as for normal pregnancy plus initial 24 h urine protein and creatinine clearance, retinal exam, HbA1c
  - HbA1c >140% of pre-pregnancy value associated with increased risk of spontaneous abortion and congenital malformations
- increased fetal surveillance (BPP, NST), consider fetal ECHO to look for cardiac abnormalities

Labor
- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose, and blood pressure control)
- can wait for spontaneous labor if blood glucose well-controlled and BPP normal
- induce by 40 wk
  - type of delivery
    - increased risk of cephalopelvic disproportion (CPD) and shoulder dystocia with babies >4,000 g (8.8 lbs)
    - elective C/S for predicted birthweight >4,500 g (9.9 lbs) (controversial)
- monitoring
  - during labor monitor blood glucose q1h with patient on insulin and dextrose drip
  - aim for blood glucose between 60-120 mg/dL to reduce the risk of neonatal hypoglycemia

Postpartum
- insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
- no insulin is required for 48-72 h postpartum in most type 1 DM
- monitor glucose q6h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >144 mg/dL

B. GESTATIONAL DIABETES MELLITUS

Screening and Diagnosis
- all pregnant women between 24-28 wk GA (or at any stage if high risk)
- 2 screening options
  - 1-step screening with fasting 75 g OGTT; GDM if ≥1 of:
    - FPG ≥90 mg/dL
    - 1h PG ≥180 mg/dL
    - 2h PG ≥153 mg/dL
  - 2-step screening
    - Step 1: Perform a random nonfasting 50 g OGCT
      - 1h PG <140 mg/dL is normal
      - 1h PG ≥200 mg/dL is GDM
      - if 1h PG 140-200 mg/dL, proceed to Step 2
    - Step 2: Perform a fasting 75 g OGTT, GDM if ≥1 of:
      - FPG ≥95 mg/dL
      - 1h PG ≥190 mg/dL
      - 2h PG ≥162 mg/dL

Risk Factors for GDM
- Age >25 yr
- Obesity
- Ethnicity (Aboriginal, Hispanic, Asian, African)
- FHx of DM
- Previous history of GDM
- Previous child with birthweight >4.0 kg
- Polycystic ovarian syndrome
- Current use of glucocorticoids
- Essential HTN or pregnancy-related HTN

Management
- first line is management through diet modification and increased physical activity
- initiate insulin therapy if glycemic targets not achieved within 2 wk of lifestyle modification alone
- glycemic targets: FPG <95 mg/dL, 1h PG <140 mg/dL, 2h PG <120 mg/dL

Monitoring Glucose Levels
- Frequent measurements of blood glucose during pregnancy are advised for women with type 1 or 2 DM to help prevent or treat both hypoglycemia and hyperglycemia, and also improves neonatal outcome
- Aim for FPG ≤95 mg/dL, 1 h post prandial
  - PG ≤140 mg/dL, 2 h post prandial PG ≤120 mg/dL
- Most women can be followed with monthly HbA1c determinations
• use of oral agents can be used in pregnancy but is off-label and should be discussed with patient
• stop insulin and diabetic diet postpartum
• follow-up with 75 g OGTT 6 wk-6 mo postpartum

Prognosis
• most maternal and fetal complications are related to hyperglycemia and its effects

Long-Term Maternal Complications
• type 1 and type 2 DM: risk of progressive retinopathy and nephropathy
• GDM: 50% risk of developing type 2 DM in next 20 yr

Table 11. Complications of DM in Pregnancy

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric</td>
<td>Growth Abnormalities</td>
</tr>
<tr>
<td>• HTN/preeclampsia (especially if pre-existing</td>
<td>• Macrosomia: maternal hyperglycemia leads to</td>
</tr>
<tr>
<td>nephropathy/proteinuria): insulin</td>
<td>fetal hyperinsulinism resulting in accelerated</td>
</tr>
<tr>
<td>resistance is implicated in etiology of HTN</td>
<td>anabolism</td>
</tr>
<tr>
<td>• Polyhydramnios: maternal hyperglycemia</td>
<td>• IUGR: due to placental vascular insufficiency</td>
</tr>
<tr>
<td>leads to fetal hyperglycemia, which</td>
<td></td>
</tr>
<tr>
<td>leads to fetal polyuria (a major source</td>
<td></td>
</tr>
<tr>
<td>of amniotic fluid)</td>
<td></td>
</tr>
<tr>
<td>Diabetic Emergencies</td>
<td>Delayed Organ Maturity</td>
</tr>
<tr>
<td>• Hypoglycemia</td>
<td>• Fetal lung immaturity: hyperglycemia interferes</td>
</tr>
<tr>
<td>• Ketoadiabetes</td>
<td>with surfactant synthesis (respiratory</td>
</tr>
<tr>
<td>• Diabetic coma</td>
<td>distress syndrome)</td>
</tr>
<tr>
<td>End-Organ Involvement or Deterioration</td>
<td>Congenital Anomalies (occur in type 1 DM and</td>
</tr>
<tr>
<td>(occur in type 1 DM and type 2 DM, not in GDM)</td>
<td>type 2 DM, not in GDM)</td>
</tr>
<tr>
<td>• Retinopathy</td>
<td>• 2-7x increased risk of cardiac (VSD), NTD,</td>
</tr>
<tr>
<td>• Nephropathy</td>
<td>GU (cystic kidneys), GI (anal atresia), and</td>
</tr>
<tr>
<td>Other</td>
<td>MSK (sacral agenesis) anomalies due to</td>
</tr>
<tr>
<td>• Pyelonephritis/UTI: glucosuria provides</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td>a culture medium for E. coli and other</td>
<td>• Note: Pregnancies complicated by GDM do not</td>
</tr>
<tr>
<td>bacteria</td>
<td>manifest an increased risk of congenital</td>
</tr>
<tr>
<td>• Increased incidence of spontaneous</td>
<td>anomalies because GDM develops after the</td>
</tr>
<tr>
<td>abortion (in type 1 DM and type 2 DM,</td>
<td>critical period of organogenesis (in T1)</td>
</tr>
<tr>
<td>not in GDM): related to pre-conception</td>
<td></td>
</tr>
<tr>
<td>glycomic control</td>
<td></td>
</tr>
</tbody>
</table>

Hypertension in Pregnancy
• hypertensive disorders of pregnancy are classified as either pre-existing or gestational HTN

PRE-EXISTING HYPERTENSION

Definition
• HTN (>140/90) prior to 20 wk GA, persisting >7 wk postpartum
• essential HTN is associated with an increased risk of gestational HTN, abruptio placentae, IUGR, and IUFD

GESTATIONAL HYPERTENSION

Definition
• sBP >140 or dBP >90 developing after 20th wk GA in a woman known to be normotensive before pregnancy

Risk Factors
• maternal factors
  ▪ primigravida (80-90% of gestational HTN)
  ▪ first conception with a new partner
  ▪ PMHx or FHx of gestational HTN
  ▪ DM, chronic HTN, or renal insufficiency
  ▪ Antiphospholipid syndrome
  ▪ extremes of maternal age (<18 or >35 yr)
• fetal factors
  ▪ IUGR or oligohydramnios, GTN, multiple gestation, fetal hydrops
  ▪ previous stillbirth or IUFD
Clinical Evaluation of Hypertension in Pregnancy

- in general, clinical evaluation should include the mother and fetus

evaluation of mother

- body weight
- central nervous system
  - presence and severity of headache
  - visual disturbances – blurring, scotomata
  - tremulousness, irritability, somnolence
  - hyperreflexia
- hematologic
  - bleeding, petechiae
- hepatic
  - RUQ or epigastric pain
  - severe N/V
- renal
  - urine output and color
  - non-dependent edema (i.e. hands and face)

evaluation of fetus

- fetal movement
- fetal heart rate tracing – NST
- ultrasound for growth
  - BPP
  - Doppler flow studies

Laboratory Evaluation of Gestational Hypertension

- hemoglobin, platelets, blood film
- PTT, INR, fibrinogen – especially if surgery or regional anesthetics are planned
- ALT, AST, LDH, bilirubin
- proteinuria, creatinine, uric acid
- 24 h urine collection for total protein and creatinine clearance or spot urine protein:creatinine ratio

Complications

- maternal
  - liver and renal dysfunction
  - seizure
  - abruptio placenta
  - left ventricular failure/pulmonary edema
  - DIC (release of placental thromboplastin consumptive coagulopathy)
  - HELLP syndrome
    - treat with FFP infusion or plasma exchange
    - hemorrhagic stroke (50% of deaths)
  - fetal (2nd to placental insufficiency)
    - IUGR, prematurity, abruptio placenta, IUFD

Management

- target a BP of 130-155/80-105 in women without comorbidities or 130-139/80-89 in women with comorbidities
- for both pre-existing and gestational HTN, labetalol 100-400 mg PO bid-tid, nifedipine (PA tablets 10-20 mg PO bid-tid or XL preparation 20-60 mg PO daily), or α-methyldopa 250-500 mg PO tid-qid
- for severe HTN (BP >160/110), give one of
  - labetalol 20 mg IV then 20-80 mg IV q30min (max 300 mg)
  - nifedipine 5-10 mg capsule q30min
  - hydralazine 5 mg IV, repeat 5-10 mg IV q30min (max 20 mg IV)
- no ACE inhibitors, ARBs, diuretics, prazosin, or atenolol
- pre-existing HTN and gestational HTN without any deterioration can be followed until 37 wk then decide to induce shortly thereafter

PREECLAMPSIA

Definition

- pre-existing or gestational HTN with new onset proteinuria or adverse conditions

Risk Factors

- nulliparity
- preeclampsia in a previous pregnancy
- age >40 yr or <18 yr
- FHx of preeclampsia

Hypertension in Pregnancy

- Adverse Maternal Conditions
  - sSBP > 160 mmHg
  - dSBP > 100 mmHg
  - HELLP
  - Cerebral hemorrhage
  - Renal dysfunction: oliguria <500 mL/d
  - Left ventricular failure, pulmonary edema
  - Placental abruption, DIC

- Symptoms
  - Abdominal pain, N/V
  - Headaches, visual problems
  - SOB, chest pain
  - Eclampsia: convulsions

- Adverse Fetal Conditions
  - Intrauterine growth restriction
  - Oligohydramnios
  - Absent/reversed umbilical artery end diastolic flow

- Can result in
  - Fetal disability and/or death
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- chronic HTN
- chronic renal disease
- antiphospholipid antibody syndrome or inherited thrombophilia
- vascular or connective tissue disease
- DM (pre-gestational and gestational)
- high BMI
- hydrops fetalis
- unexplained fetal growth restriction
- abruptio placentae
- there is a potential for further deterioration to severe preeclampsia as defined above
- the adverse conditions are many and include both maternal and fetal issues

**Management**
- management will depend on GA, possible threat of seizures (check reflexes)
- if stable and no adverse factors, may admit and follow, ± decide to deliver as approaching 34-36 wk (must weigh risks of fetal prematurity vs. risks of developing severe preeclampsia/eclampsia)
- for severe preeclampsia, stabilize and deliver
- if severe preeclampsia, during labor, increase maternal monitoring: hourly input and output, urine dip q12h, hourly neurological vitals, and increase fetal monitoring (continuous FHR monitoring)
- antihypertensive therapy
  - lowering BP decreases the risk of stroke
  - hydralazine 5-10 mg IV bolus over 5 min q15-30min as necessary
  - labetalol 20-50 mg IV q10min
  - 2nd line: nifedipine 10-20 mg PO q20-60min
- seizure prevention
  - MgSO₄
  - postpartum management
  - risk of seizure highest in first 24 h postpartum – continue MgSO₄ for 12-24 h after delivery
  - vitals q1h
  - consider HELLP syndrome in toxic patients
  - most return to a normotensive BP within 2 wk

**ECLAMPSIA**

**Definition**
- the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions

**Epidemiology**
- an eclamptic seizure occurs in approximately 0.5% of mildly preeclamptic women and 2-3% of severely preeclamptic women

**Risk Factors**
- same as risk factors for preeclampsia

**Clinical Manifestations**
- eclampsia is a clinical diagnosis
- typically tonic-clonic and lasting 60-75 s
- one of the signs of an impending seizure is hyperreflexia
- symptoms that may occur before the seizure include persistent frontal or occipital headache, blurred vision, photophobia, right upper quadrant or epigastric pain, and altered mental status
- in up to one third of cases, there is no proteinuria or blood pressure is <140/90 mmHg prior to the seizure
- in general, women with typical eclamptic seizures who do not have focal neurologic deficits or prolonged coma do not require diagnostic evaluation including imaging

**Management**
- ABCs
- roll patient into LLDP
- supplemental O₂ via face mask to treat hypoxemia due to hypoventilation during convulsive episode
- aggressive antihypertensive therapy for sustained diastolic pressures ≥105 mmHg or systolic blood pressures ≥160 mmHg with hydralazine or labetalol
- prevention of recurrent convulsions: to prevent further seizures and the possible complications of repeated seizure activity (e.g. rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, etc.)
- MgSO₄ is now the drug of choice, with previously used agents including diazepam and phenytoin

**Preeclampsia Investigations**

- CBC
- LDH
- Liver enzymes
- INR and aPTT
- Cr
- Uric acid
- Protein/creatinine ratio

**HELLP Syndrome**
- Hemolysis
- Elevated Liver enzymes
- Low Platelets

**Differential Diagnosis of Cause for Seizure in a Pregnant Woman**
- Stroke
- Hypertensive disease (hypertensive encephalopathy, pheochromocytoma)
- Space-occupying lesion of the CNS
- Metabolic disorders (hypoglycemia, SIADH)
- Infection (meningitis, encephalitis)
- Thrombotic thrombocytopenic purpura or thrombophilia
- Idiopathic epilepsy
- Use of illicit drugs
- Cerebral vasculitis

**Note**
- Eclampsia prior to 20 wk of gestation is rare and should raise the possibility of an underlying molar pregnancy or antiphospholipid syndrome

**MgSO₄ Toxicity**
- Flushing
- Hyporeflexia
- Somnolence
- Respiratory and cardiac depression
- Weakness

**Note**
- Increased risk of toxicity with concurrent calcium channel blocker use or renal disease

**Treatment**
- Stop MgSO₄
- Calcium gluconate 10% in 10 mL IV
the definitive treatment of eclampsia is DELIVERY, irrespective of gestational age, to reduce the risk of maternal morbidity and mortality from complications of the disease
mode of delivery is dependent on clinical situation and fetal-maternal condition

### Nausea and Vomiting

#### Epidemiology
- affects 50-90% of pregnant women
- often limited to T1 but may persist

#### Management
- rule out other causes of N/V
- weigh frequently, assess level of hydration, test urine for ketones
- **non-pharmacological**
  - avoid mixing fluids and solids, frequent small meals
  - stop prenatal vitamins (folic acid must continue until >12 wk)
  - increase sleep/rest
  - ginger (maximum 1,000 mg/d)
  - acupuncture, acupressure
- **pharmacological**
  - first line: Diclectin’ (10 mg doxylamine succinate with vitamin B6) 4 tablets PO daily to maximum of 8 tablets
  - if no improvement, try dimenhydrinate (50-100 mg q4-6h PO), followed by hydroxyzine, pyridoxine, phenothiazine, or metoclopramide
  - vitamin B6 lollipops
  - if patient dehydrated, assess fluid replacement needs and resuscitate accordingly
- **severe/refractory:**
  - consider homecare with IV fluids and parenteral anti-emetics, hospitalization

### Hyperemesis Gravidarum

#### Definition
- intractable N/V, usually presents in T1 then diminishes; occasionally persists throughout pregnancy
- affects ~1% of pregnancies

#### Etiology
- multifactorial with hormonal, immunologic, and psychologic components
- rapidly rising β-hCG ± estrogen levels may be implicated

#### Investigations
- rule out systemic causes: GI inflammation, pyelonephritis, thyrotoxicosis
- rule out obstetrical causes: multiple gestation, GTN, HELLP syndrome
- CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
- ultrasound

#### Management
- thiamine supplementation may be indicated
- **non-pharmacological** *(see Nausea and Vomiting)*
- **pharmacological options** *(see Nausea and Vomiting)*
  - Diclectin’ (for dosage, see Nausea and Vomiting)
  - Dimenhydrinate can be safely used as an adjunct to Diclectin’ (1 suppository bid or 25 mg PO qid)
  - other adjuncts: hydroxyzine, pyridoxine, phenothiazine, metoclopramide
  - also consider: ondansetron or methylprednisolone
  - if severe: admit to hospital, NPO initially then small frequent meals, correct hypovolemia, electrolyte disturbance, and ketosis, TPN (if very severe) to reverse catabolic state

#### Complications
- maternal
  - dehydration, electrolyte and acid-base disturbances
  - Mallory-Weiss tear
  - Wernicke’s encephalopathy, if protracted course
  - death
- fetal: usually none, IUGR is 15x more common in women losing >5% of pre-pregnancy weight
**Urinary Tract Infection**

**Etiology**
- Increased urinary stasis from mechanical and hormonal (progesterone) factors
- Organisms include GBS as well as those that occur in non-pregnant women

**Epidemiology**
- Most common medical complication of pregnancy
- Asymptomatic bacteriuria in 2-7% of pregnant women, more frequently in multiparous women
- Note: Asymptomatic bacteriuria should be treated in pregnancy due to increased risk of pyelonephritis

**Clinical Features**
- May be asymptomatic
- Dysuria, urgency, and frequency in cystitis
- Fever, flank pain, and costovertebral angle tenderness in pyelonephritis

**Investigations**
- Urinalysis, urine C&S
- Cystoscopy, and renal function tests in recurrent infections

**Management**
- Uncomplicated UTI
  - First line: amoxicillin (250-500 mg PO q8h x 7 d)
  - Alternatives: nitrofurantoin (100 mg PO bid x 7 d)
  - Follow with monthly urine cultures
- Pyelonephritis
  - Hospitalization and IV antibiotics

**Prognosis**
- Complications if untreated: acute cystitis, pyelonephritis, and possible preterm labor
- Recurrence is common

---

### Infections During Pregnancy

**Table 12. Infections During Pregnancy**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent</th>
<th>Source of Transmission</th>
<th>Greatest Transmission Risk to Fetus</th>
<th>Effects on Fetus</th>
<th>Effects on Mother</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chicken Pox</td>
<td>Varicella zoster virus</td>
<td>To mom: direct, respiratory To baby: transplacental</td>
<td>13-30 wk GA, and 5 d pre- to 2 d post-delivery</td>
<td>Congenital varicella syndrome (limb aplasia, chorioretinitis, cutaneous scars, cortical atrophy, IUGR, hydrops), preterm labor (prematurity)</td>
<td>Fever, malaise, vesicular puritic lesions</td>
<td>Clinical, ± vesicle fluid culture, ± serology</td>
<td>VZIG for mother if exposed, decreases congenital varicella syndrome Note: do not administer vaccine during pregnancy (live attenuated)</td>
</tr>
<tr>
<td><em>CMV</em></td>
<td>DNA virus (herpes family)</td>
<td>To mom: blood/organ transfusion, sexual contact To baby: transplacental during delivery, breast milk</td>
<td>T1-T3</td>
<td>5-10% develop CNS involvement (mental retardation, cerebral calcification, hydrocephalus, microcephaly, deafness, chorioretinitis)</td>
<td>Asymptomatic or flu-like</td>
<td>Serologic screen; isolate virus from urine or secretion culture</td>
<td>No specific treatment; maintain good hygiene and avoid high risk situations</td>
</tr>
<tr>
<td>Erythema Infectiosum (Fifth Disease)</td>
<td>Parvovirus B19</td>
<td>To mom: respiratory, infected blood products To baby: transplacental</td>
<td>10-20 wk GA</td>
<td>Spontaneous abortion (SA), stillbirth, hydrops in utero</td>
<td>Flu-like, rash, arthritis; often asymptomatic</td>
<td>Serology, viral PCR, maternal AFP; if IgM present, follow fetus with U/S for hydrops</td>
<td>If hydrops occurs, consider fetal transfusion</td>
</tr>
</tbody>
</table>
### Table 12. Infections During Pregnancy (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent</th>
<th>Source of Transmission</th>
<th>Greatest Transmission Risk to Fetus</th>
<th>Effects on Fetus</th>
<th>Effects on Mother</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>DNA virus</td>
<td>To mom: blood, saliva, semen, vaginal secretions To baby: transplacental, breast milk</td>
<td>T3 10% vertical transmission if asymptomatic and HBsAg +ve; 85-90% if HBsAg and HBsAg +ve</td>
<td>Prematurity, low birth weight, neonatal death</td>
<td>Fever, N/V, fatigue, jaundice, elevated liver enzymes</td>
<td>Serologic screening for all pregnancies</td>
<td>Rx neonate with HBIG and vaccine (at birth, 1, 6 mo); 90% effective</td>
</tr>
<tr>
<td><em>Herpes Simplex Virus</em></td>
<td>DNA virus</td>
<td>To mom: intimate mucocutaneous contact To baby: transplacental, during delivery</td>
<td>Delivery (if genital lesions present); less commonly in utero</td>
<td>Disseminated herpes (20%); CNS sequelae (35%); self-limited infection</td>
<td>Painful vesicular lesions</td>
<td>Clinical diagnosis</td>
<td>Acyclovir for symptomatic women, suppressive therapy at 36 wk controversial C/S if active genital lesions, even if remote from vulva</td>
</tr>
<tr>
<td>HIV</td>
<td>RNA retrovirus</td>
<td>To mom: blood, semen, vaginal secretions To baby: in utero, during delivery; breast milk</td>
<td>1/3 in utero, 1/3 at delivery, 1/3 breastfeeding</td>
<td>IUGR, preterm labor, PROM</td>
<td>See Infectious Diseases, ID29</td>
<td>Serology, viral PCR All pregnant women are offered screening</td>
<td>Triple antiretroviral therapy decreases transmission to &lt;1% Elective C/S: no previous antiviral Rx or monotherapy only, viral load unknown or &gt;500 RNA copies/mL, unknown prenatal care, patient request</td>
</tr>
<tr>
<td><em>Rubella</em></td>
<td>ssRNA togavirus</td>
<td>To mom: respiratory droplets (highly contagious) To baby: transplacental</td>
<td>T1</td>
<td>SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, MR, IUGR, hepatitis, CNS defects, osseous changes)</td>
<td>Rash (50%), fever, posterior auricular or occipital lymphadenopathy, arthralgia</td>
<td>Serologic testing; all pregnant women screened (immune if titre &gt;1:16); infection if IgM present or &gt;4x increase in IgG</td>
<td>No specific treatment; offer vaccine following pregnancy Do not administer during pregnancy (live attenuated)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Spirochete (Treponema pallidum)</td>
<td>To mom: sexual contact To baby: transplacental</td>
<td>T1-T3</td>
<td>Risk of preterm labor, multisystem involvement, fetal death</td>
<td>See Infectious Diseases, ID26</td>
<td>VDRL screening for all pregnancies; if positive, requires confirmatory testing</td>
<td>Pen G 2.4 M U IM 1 dose if early syphilis, 3 doses if late syphilis, monitor VDRL monthly If Pen G allergic: Cldamycin 900 mg IV q8h</td>
</tr>
<tr>
<td><em>Toxoplasmosis</em></td>
<td>Protozoa (Toxoplasma gondii)</td>
<td>To mom: raw meat, unpasteurized goat’s milk, cat feces/urine To baby: transplacental</td>
<td>T3 (but most severe if infected in T1); only concern if primary infection during pregnancy</td>
<td>Congenital toxoplasmosis (chorioretinitis, hydrocephaly, intracranial calcification, MR, microcephaly) NB: 75% initially asymptomatic at birth</td>
<td>Majority subclinical; may have flu-like symptoms</td>
<td>IgM and IgG serology; PCR of amniotic fluid</td>
<td>Self-limiting in mother; spiramycin decreases fetal morbidity but not rate of transmission</td>
</tr>
</tbody>
</table>

* * Indicates TORCH infection

---

**Venous Thromboembolism**

**Epidemiology**
- incidence 0.5-3/1,000 pregnancies occurring with approximately equal frequency in all three trimesters and postpartum

**Risk Factors**
- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, thrombophilies (see Hematology, H33)
Table 13. Risk Factors for VTE Specific to Pregnancy

<table>
<thead>
<tr>
<th>Hypercoagulability</th>
<th>Stasis</th>
<th>Endothelial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased factors: II, V, VII, VIII, IX, X, XII, fibrinogen</td>
<td>Increased resistance to activated protein C</td>
<td>Vascular damage at delivery (C/S or SVD)</td>
</tr>
<tr>
<td>Increased platelet aggregation</td>
<td>Antithrombin can be normal or reduced</td>
<td>Uterine instrumentation</td>
</tr>
<tr>
<td>Decreased protein S, tPA, factors XI, XII</td>
<td>Increased venous distensibility</td>
<td>Peripartum pelvic surgery</td>
</tr>
<tr>
<td></td>
<td>Decreased venous tone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50% decrease in venous flow in lower extremity by T3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uterus is mechanical impediment to venous return</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a pulmonary embolism are non-specific (as in non-pregnant women)
- unexplained spontaneous fetal loss

Investigations
- duplex venous Doppler sonography for DVT
- CXR and V/Q scan or spiral CT for PE

Management
- before initiating treatment, obtain a baseline CBC including platelets, and aPTT
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- unfractionated heparin
  - bolus of 5,000 IU followed by an infusion of ~30,000 IU/24h
  - measure aPTT 6 h after the bolus
  - maintain aPTT at a therapeutic level (1.5-2x normal)
  - repeat q24h once therapeutic
  - heparin-induced thrombocytopenia (HIT) uncommon (3%) but serious complication
  - LMWH can also be used in pregnancy
- compression stockings
- poor evidence to support a recommendation for or against avoidance of prolonged sitting
- VTE prophylaxis
  - women on long-term anticoagulation: full therapeutic anticoagulation throughout pregnancy and for 6-12 wk postpartum
  - women with a non-active PMHx of VTE: unfractionated heparin regimens suggested
- routine VTE prophylaxis
  - insufficient evidence in pregnancy to recommend routine use of LMWH
  - current prophylaxis regimens for acquired thrombophilias (e.g. APS syndrome) include low dose Aspirin® in conjunction with prophylactic heparin

Bleeding in Pregnancy

First and Second Trimester Bleeding

Approach to the Patient with Bleeding in T1/T2
- history
  - risk factors for ectopic pregnancy (previous ectopic pregnancies, history of STD/PID, IUD use, previous pelvic surgery, smoking)
  - previous spontaneous abortion
  - recent trauma
  - characteristics of the bleeding (including any tissue passed)
  - characteristics of the pain (cramping pain suggests SA)
  - history of coagulopathy
  - gynecological/obstetric history
  - dizziness (significant blood loss, may be associated with ruptured ectopic)
  - fever (may be associated with septic abortion)
- physical
  - vitals (including orthostatic changes)
  - abdomen (SFH, tenderness, presence of contractions)
  - perineum (signs of trauma, genital lesions)
  - speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
  - pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness)
Investigations
- β-hCG (lower than expected for GA in spontaneous abortion, ectopic pregnancy)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

Treatment
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

Spontaneous Abortions

Table 14. Classification of Spontaneous Abortions

<table>
<thead>
<tr>
<th>Type</th>
<th>History</th>
<th>Clinical</th>
<th>Management (+ Rhogam®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened</td>
<td>Vaginal bleeding ± cramping</td>
<td>Cervix closed and soft</td>
<td>Watch and wait</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U/S shows viable fetus</td>
<td>&lt;5% go on to abort</td>
</tr>
<tr>
<td>Inevitable</td>
<td>Increasing bleeding and cramps</td>
<td>Cervix closed until products</td>
<td>a) Watch and wait</td>
</tr>
<tr>
<td></td>
<td>± rupture of membranes</td>
<td>start to expel, then external</td>
<td>b) Misoprostol 400-800 µg P0/PV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>os opens</td>
<td>c) D&amp;C ± oxytocin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U/S variable but usually</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>nonviable fetus</td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>Extremely heavy bleeding</td>
<td>Cervix open</td>
<td>a) Watch and wait</td>
</tr>
<tr>
<td></td>
<td>and cramps ± passage of tissue</td>
<td>U/S products of conception</td>
<td>b) Misoprostol 400-800 µg P0/PV</td>
</tr>
<tr>
<td></td>
<td>noticed</td>
<td>c) D&amp;C ± oxytocin</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>Bleeding and complete passage</td>
<td>Cervix open</td>
<td>No D&amp;C – expectant management</td>
</tr>
<tr>
<td></td>
<td>of sac and placenta</td>
<td>U/S no products of conception</td>
<td></td>
</tr>
<tr>
<td>Missed</td>
<td>No bleeding (fetal death in utero)</td>
<td>Cervix closed</td>
<td>a) Watch and wait</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U/S may show SGA, no fetal</td>
<td>b) Misoprostol 400-800 µg P0/PV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>heart activity; nonviable fetus</td>
<td>c) D&amp;C ± oxytocin</td>
</tr>
<tr>
<td>Recurrent</td>
<td>≥3 consecutive spontaneous</td>
<td></td>
<td>Evaluate mechanical, genetic,</td>
</tr>
<tr>
<td></td>
<td>abortions</td>
<td></td>
<td>environmental, and other risk factors</td>
</tr>
<tr>
<td>Septic</td>
<td>Contents of uterus infected</td>
<td>D&amp;C</td>
<td>IV broad spectrum antibiotics</td>
</tr>
</tbody>
</table>

Ectopic Pregnancy

Definition
- embryo implants outside of the endometrial cavity

Epidemiology
- 1/100 pregnancies
- fourth leading cause of maternal mortality, leading cause of death in first trimester
- increase in incidence over the last 3 decades
- three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)

Etiology
- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigiration of fertilized ovum to contralateral tube
Figure 3. Sites of ectopic pregnancy implantation

Ampullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

Risk Factors
- previous ectopic pregnancy
- gynecologic
  - IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with C. trachomatis), salpingitis
  - infertility
  - clomiphene citrate (for induction of ovulation)
- previous procedures
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
  - IVF pregnancies following ovulation induction (7% ectopic rate)
- smoking
- structural
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

Investigations
- serial β-hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
- rise of <20% of β-hCG is 100% predictive of a non-viable pregnancy
- prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
- 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - specific finding on transvaginal U/S is a tubal ring
- laparoscopy (for definitive diagnosis)

Treatment
- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical (laparoscopy)
  - linear salpingostomy if tube salvageable
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
  - 15% risk of persistent trophoblast; must monitor β-hCG titres weekly until they reach non-detectable levels
- consider Rhogam® if Rh negative
- may require laparotomy if patient is unstable, extensive abdominal surgical history, etc.
- medical = methotrexate (for indications see Figure 4)
  - use 50 mg/m² body surface area; given in a single IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)

DDx of Lower Abdominal Pain
- Urinary tract: UTI, kidney stones
- GI: diverticulitis, appendicitis
- Gyne: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

If Ectopic Pregnancy Ruptures
- Acute abdomen with increasing pain
- Abdominal distention
- Shock
- follow β-hCG levels weekly until β-hCG is non-detectable
- plateau or rising levels suggest persisting trophoblastic tissue (requires further treatment)
- 82-95% success rate but up to 25% will require a second dose
- tubal patency following methotrexate treatment approaches 80%

**Prognosis**
- 9% of maternal deaths during pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

**Interventions for Tubal Ectopic Pregnancy**
*Study:* Cochrane Review of randomized controlled trials comparing treatments in women with tubal ectopic pregnancy.
*Patients:* Women with a diagnosis of tubal ectopic pregnancy.
*Intervention:* Surgery (salpingectomy/salpingostomy by open surgery or by laparoscopy), medical treatment, and expectant management.
*Main Outcome:* Primary treatment success, defined as an uneventful decline in serum β-hCG to undetectable levels by the initial treatment.
*Results:* Intramuscular MTX therapy and salpingostomy yielded similar treatment success rates (82-95% for MTX therapy vs. 80-92% for salpingostomy).

**Antepartum Hemorrhage**

**Definition**
- vaginal bleeding from 20 wk to term

**Differential Diagnosis**
- bloody show (shedding of cervical mucous plug) – most common etiology in T3
- placenta previa
- abruptio placenta – most common pathological etiology in T3
- vasa previa
- cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
- other: bleeding from bowel or bladder, placenta accreta, abnormal coagulation

**Table 15. Comparison of Placenta Previa vs. Abruptio Placentae**

<table>
<thead>
<tr>
<th></th>
<th>Placenta Previa</th>
<th>Abruptio Placentae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Abnormal location of the placenta near, partially,</td>
<td>Premature separation of a normally implanted placenta</td>
</tr>
<tr>
<td></td>
<td>or completely over the internal cervical os</td>
<td>after 20 wk GA</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Idiopathic</td>
<td>Idiopathic</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>0.5-0.8% of all pregnancies</td>
<td>1-2% of all pregnancies</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>• History of placenta previa (4-8% recurrence risk)</td>
<td>• Previous abruption (recurrence rate 5-16%)</td>
</tr>
<tr>
<td></td>
<td>• Multiparity</td>
<td>• Maternal HTN (chronic or gestational HTN in 50%</td>
</tr>
<tr>
<td></td>
<td>• Increased maternal age</td>
<td>of abruptions) or vascular disease</td>
</tr>
<tr>
<td></td>
<td>• Multiple gestation</td>
<td>• Cigarette smoking (&gt;1 pack/d), excessive alcohol</td>
</tr>
<tr>
<td></td>
<td>• Uterine tumor (e.g. fibroids) or other uterine</td>
<td>consumption, cocaine</td>
</tr>
<tr>
<td></td>
<td>anomalies</td>
<td>• Multiparity and/or maternal age &gt; 35 yr</td>
</tr>
<tr>
<td></td>
<td>• Uterine scar due to previous abortion, C/S, D&amp;C,</td>
<td>• PPRROM</td>
</tr>
<tr>
<td></td>
<td>myomectomy</td>
<td>• Rapid decompression of a distended uterus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(polyhydraminos, multiple gestation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Uterine anomaly, fibroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Trauma (e.g. motor vehicle collision, maternal battery)</td>
</tr>
</tbody>
</table>

**Key Questions to Ask in Antepartum Hemorrhage**
- How much bleeding?
- Are there contractions/cramping/pain?
- Description? Color, clotting, etc.

**Levels of Abnormal Placental Invasion**
- Placenta Accreta: AT myometrium (most common)
- Placenta Increta: INTO myometrium
- Placenta Percreta: PASSES through myometrium
Placenta Previa

Definition
- Placenta implanted in the lower segment of the uterus, presenting ahead of the leading pole of the fetus
- The distance of the placental edge from the internal os is described in “millimeters away” from the internal os or “millimeters of overlap” over the internal os
- Greater than 20 millimeters of overlap over the internal os in the third trimester of pregnancy is highly predictive of the need for a C/S
- Any degree of overlap after 35 wk is an indication for a C/S

Clinical Features
- Painless bright red vaginal bleeding (recurrent), may be minimized and cease spontaneously, but can become catastrophic
- Mean onset of bleeding is 30 wk GA, but onset depends on degree of previa
- Physical exam
  - Uterus soft and non-tender
  - Presenting fetal part high or displaced
  - FHR usually normal
  - Shock/anemia correspond to degree of apparent blood loss
- Complications
  - Fetal
    - Perinatal mortality low but still higher than with a normal pregnancy
    - Prematurity (bleeding often dictates early C/S)
    - Intrauterine hypoxia (acute or IUGR)
    - Fetal malpresentation
    - PPROM
    - Risk of fetal blood loss from placenta, especially if incised during C/S
  - Maternal
    - <1% maternal mortality
    - Hemorrhage and hypovolemic shock, anemia, acute renal failure, pituitary necrosis (Sheehan syndrome)
    - Placenta accreta – especially if previous uterine surgery, anterior placenta previa
    - Hysterectomy

Investigations
- Transvaginal U/S is more accurate than transabdominal U/S at diagnosing placenta previa at any gestational age
- If the placenta lies between 20 mm of overlap and 20 mm away from the internal os after 26 wk regular transvaginal ultrasounds should be repeated at regular intervals – continued change in the placental location is likely

Management
- Goal: keep pregnancy intrauterine until the risk of delivery < risk of continuing pregnancy
- Stabilize and monitor
  - Maternal stabilization: large bore IV with hydration, O2 for hypotensive patients
  - Maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, INR/PTT, platelets, fibrinogen, FDP, type and cross match)
  - Electronic fetal monitoring
  - U/S assessment: when fetal and maternal condition permit, determine fetal viability, gestational age, and placental status/position
- Rhogam® if mother is Rh negative
  - Kleihauer-Betke test to determine extent of fetomaternal transfusion so that appropriate dose of Rhogam® can be given
- GA <37 wk and minimal bleeding: expectant management
  - Admit to hospital
  - Limited physical activity, no douches, enemas, or sexual intercourse
  - Consider corticosteroids for fetal lung maturity
  - Delivery when fetus is mature or hemorrhage dictates
- GA ≥37 wk, profuse bleeding, or L/S ratio is >2:1 – deliver by C/S

Kleihauer-Betke Test
- Quantifies fetal cells in the maternal circulation

Do NOT perform a vaginal exam until placenta previa has been ruled out by U/S
Abruptio Placentae

Clinical Features

- classification
  - total (fetal death inevitable) vs. partial
  - external/revealed/apparent: blood dissects downward toward cervix
  - internal/concealed (20%): blood dissects upward toward fetus
  - most are mixed

- presentation
  - PAINFUL (80%) vaginal bleeding (bleeding not always present if abruption is concealed),
    uterine tenderness, uterine contractions
  - pain: sudden onset, constant, localized to lower back and uterus
  - shock/anemia out of proportion to apparent blood loss
  - ± fetal distress, fetal demise (15% present with demise), bloody amniotic fluid (fetal
    presentation typically normal)
  - ± coagulopathy

Complications

- fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
- maternal complications: <1% maternal mortality, DIC (in 20% of abruptions), acute renal
  failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), amniotic fluid
  embolus

Investigations

- clinical diagnosis, U/S not sensitive for diagnosing abruption (sensitivity = 15%)

Management

- maternal stabilization: large bore IV with hydration, O2 for hypotensive patients
- maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, PT/PT,
  platelets, fibrinogen, FDP, type and cross match)
- EFM
- blood products on hand (red cells, platelets, cryoprecipitate) because of DIC risk
- Rhogam® if Rh negative
  - Kleihauer-Betke test may confirm abruption
- mild abruption
  - GA <37 wk: use serial Hct to assess concealed bleeding, deliver when fetus is mature or when
    hemorrhage dictates
  - GA ≥37 wk: stabilize and deliver
- moderate to severe abruption
  - hydrate and restore blood loss and correct coagulation defect if present
  - vaginal delivery if no contraindication and no evidence of fetal or maternal distress OR fetal
    demise
  - C/S if live fetus and fetal or maternal distress develops with fluid/blood replacement, labor
    fails to progress or if vaginal delivery otherwise contraindicated

Vasa Previa

Definition

- unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord
  into membranes of placenta or succenturiate (accessory) lobe

Epidemiology

- 1 in 5,000 deliveries – higher in twin pregnancies

Clinical Features

- PAINLESS vaginal bleeding and fetal distress (tachy- to bradyarrhythmia)
- 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of
  exsanguination)

Investigations

- Apt test (NaOH mixed with the blood) can be done immediately to determine if the source of
  bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
- Wright stain on blood smear and look for nucleated red blood cells (in cord, not maternal
  blood)

Management

- emergency C/S (since bleeding is from fetus, a small amount of blood loss can have catastrophic
  consequences)
Multiple Gestation

Epidemiology
• incidence of twins is 1/80 and triplets 1/6,400 in North America
• 2/3 of twins are dizygotic (fraternal)
  ▪ risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, ethnicity (e.g. certain African regions)
• monozygous twinning occurs at a constant rate worldwide (1/250)
• determine zygosity by number of placentas, thickness of membranes, sex, blood type

Clinical Features

Table 16. Complications Associated with Multiple Gestation

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Uteroplacental</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>Increased PROM/PTL</td>
<td>Prematurity*</td>
</tr>
<tr>
<td>GDM</td>
<td>Polyhydramnios</td>
<td>IUGR</td>
</tr>
<tr>
<td>Gestational HTN</td>
<td>Placenta previa</td>
<td>Malpresentation</td>
</tr>
<tr>
<td>Anemia</td>
<td>Placental abruption</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Increased physiological stress on all systems</td>
<td>PPH (uterine atony)</td>
<td>Twin-twin transfusion</td>
</tr>
<tr>
<td>Increased compressive symptoms</td>
<td>Umbilical cord prolapse</td>
<td>Increased perinatal morbidity and mortality</td>
</tr>
<tr>
<td>C/S</td>
<td>Cord anomalies</td>
<td>Twin interlocking</td>
</tr>
</tbody>
</table>

*Most common cause of perinatal mortality in multiple gestation

Management
• U/S determination of chorionicity must be done within first trimester (ideally 8-12 wk GA)
• increased antenatal surveillance
  ▪ serial U/S q2-3wk from 28 wk GA to assess growth (uncomplicated diamniotic dichorionic)
  ▪ increased frequency of ultrasounds in monochorionic diamniotic and monochorionic monoamniotic twins
  ▪ Doppler flow studies weekly if discordant fetal growth (>30%)
  ▪ BPP as needed
• may attempt vaginal delivery if twin A presents as vertex, otherwise C/S (40-50% of all twin deliveries, 15% of cases have twin A delivered vaginally and twin B delivered by C/S)
• mode of delivery depends on fetal weight, GA, presentation

Figure 6. Classification of twin pregnancies

*D indicates time of cleavage
### Twin-Twin Transfusion Syndrome

**Epidemiology**
- 10% of monochorionic twins
- concern if >30% discordance in estimated fetal weight

**Etiology**
- arterial blood from donor twin passes through placenta into vein of recipient twin

**Clinical Features**
- donor twin: IUGR, hypovolemia, hypotension, anemia, oligohydramnios
- recipient twin: hypervolemia, HTN, CHF, polycythemia, edema, polyhydramnios, kernicterus in neonatal period

**Investigations**
- detected by U/S screening, Doppler flow analysis

**Management**
- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary
- laparoscopic occlusion of placental vessels

### Growth Discrepancies

#### Intrauterine Growth Restriction

**Definition**
- infant weight <10th percentile for GA or <2,500 g

**Etiology/Risk Factors**
- maternal causes
  - malnutrition, smoking, drug abuse, alcoholism, cyanotic heart disease, type 1 DM, SLE, pulmonary insufficiency, previous IUGR
- maternal-fetal
  - any disease causing placental insufficiency
  - includes gestational HTN, chronic HTN, chronic renal insufficiency, gross placental morphological abnormalities (infarction, hemangiomas)
- fetal causes:
  - TORCH infections, multiple gestation, congenital anomalies

**Clinical Features**
- symmetric/type I (20%): occurs early in pregnancy
  - inadequate growth of head and body
  - head:abdomen ratio may be normal (>1 up to 32 wk; =1 at 32-34 wk; <1 after 34 wk GA)
  - usually associated with congenital anomalies or TORCH infections
- asymmetric/type II (80%): occurs late in pregnancy
  - brain is spared, therefore head:abdomen ratio increased
  - usually associated with placental insufficiency
  - more favorable prognosis than type I
- complications
  - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, and mental retardation
  - greater risk of perinatal morbidity and mortality

**Investigations**
- SFH measurements at every antepartum visit
- if mother at high risk or SFH lags >2 cm behind GA
  - U/S for biparietal diameter, head and abdominal circumference, femur length, fetal weight, and AFV (decrease associated with IUGR)
  - ± BPP
  - Doppler analysis of umbilical cord blood flow

**Management**
- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition, and treat maternal illness
- bed rest in LLDP
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if GA >34 wk
- liberal use of C/S since IUGR fetus withstands labor poorly

**TORCH**
- Toxoplasmosis
- Others: e.g. syphilis
- Rubella
- CMV
- HSV

**Differential Diagnosis of Incorrect Uterine Size for Dates**
- Inaccurate dates
- Maternal: DM
- Maternal-fetal: polyhydramnios, oligohydramnios
- Fetal: abnormal karyotype, IUGR, macrosomia, fetal anomaly, abnormal lie, multiple gestation

**Monitoring Fetal Growth with U/S**
- Done biweekly to show growth beyond the margin of error
Macrosomia

Definition
- infant weight >90th percentile for a particular GA or >4,000 g

Etiology/Risk Factors
- maternal obesity, GDM, past history of macrosomic infant, prolonged gestation, multiparity

Clinical Features
- increased risk of perinatal mortality
- CPD and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labor (see Table 11, OB15)

Investigations
- serial SFH
- further investigations if mother at high risk or SFH >2 cm ahead of GA
- U/S predictors
  - polyhydramnios
  - third trimester AC >1.5 cm/wk
  - HC/AC ratio <10th percentile
  - FL/AC ratio <20th percentile

Management
- prophylactic C/S is a reasonable option where EFW >5,000 g in non-diabetic woman and EFW >4,500 g in diabetic woman
- no evidence that prophylactic C/S improves outcomes
- early induction of labor is not recommended for non-diabetic mothers
- risks and benefits of early induction (risk of C/S vs. risk of dystocia) must be weighed in diabetic mothers, as current research is unclear

Polyhydramnios/Oligohydramnios

Table 17. Polyhydramnios and Oligohydramnios

<table>
<thead>
<tr>
<th>Polyhydramnios</th>
<th>Oligohydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>AFI &gt;25 cm</td>
</tr>
<tr>
<td></td>
<td>U/S: single deepest pocket &gt;8 cm</td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic most common</td>
</tr>
<tr>
<td>Maternal:</td>
<td>Type 1 DM: abnormalities of transchorionic flow</td>
</tr>
<tr>
<td></td>
<td>Chorioangiomas</td>
</tr>
<tr>
<td></td>
<td>Multiple gestation</td>
</tr>
<tr>
<td>Fetal:</td>
<td>Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios)</td>
</tr>
<tr>
<td></td>
<td>Respiratory: cystic adenomatoid malformed lung</td>
</tr>
<tr>
<td></td>
<td>CNS: anencephaly, hydrocephalus, meningcele</td>
</tr>
<tr>
<td></td>
<td>GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfere with swallowing)</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Occur in 0.2-1.6% of all pregnancies</td>
</tr>
<tr>
<td>Clinical Features and Complications</td>
<td>Uterus large for dates, difficulty palpating fetal parts and hearing FHR</td>
</tr>
<tr>
<td>Maternal:</td>
<td>Pressure symptoms from overdistended uterus (dyspnea, edema, hydrenephrosis)</td>
</tr>
<tr>
<td>Obstetrical complications:</td>
<td>Cord prolapse, placental abruption, malpresentation, preterm labor, uterine dysfunction, and PPH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oligohydramnios</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>AFI &lt;5 cm</td>
</tr>
<tr>
<td>U/S: single deepest pocket ≤2 cm</td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>Idiopathic most common</td>
</tr>
<tr>
<td>Maternal:</td>
<td>Uteroplacental insufficiency (preeclampsia, nephropathy)</td>
</tr>
<tr>
<td>Fetal:</td>
<td>Congenital urinary tract anomalies (renal agenesis, obstruction, posterior urethral valves)</td>
</tr>
<tr>
<td></td>
<td>Demise/chronic hypoxemia (blood shunt away from kidneys to perfuse brain)</td>
</tr>
<tr>
<td></td>
<td>IUUG</td>
</tr>
<tr>
<td></td>
<td>Ruptured membranes: prolonged amniotic fluid leak</td>
</tr>
<tr>
<td></td>
<td>Amniotic fluid normally decreases after 35 wk</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Occur in ~4.5% of all pregnancies</td>
</tr>
<tr>
<td>Clinical Features and Complications</td>
<td>Uterus small for dates</td>
</tr>
<tr>
<td>Fetal complications:</td>
<td></td>
</tr>
<tr>
<td>Obstetrical complications:</td>
<td>Cord compression</td>
</tr>
<tr>
<td></td>
<td>Increased risk of adverse fetal outcomes</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypoplasia (late-onset)</td>
</tr>
<tr>
<td></td>
<td>Marker for infants who may not tolerate labor well</td>
</tr>
</tbody>
</table>
Table 17. Polyhydramnios and Oligohydramnios (continued)

<table>
<thead>
<tr>
<th>Polyhydramnios</th>
<th>Oligohydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Management</strong></td>
<td><strong>Always warrants admission and investigation:</strong></td>
</tr>
<tr>
<td>Determine underlying cause:</td>
<td>• Rule out ROM</td>
</tr>
<tr>
<td>• Screen for maternal disease/infection</td>
<td>• Fetal monitoring (NST, BPP)</td>
</tr>
<tr>
<td>• Complete fetal US evaluation</td>
<td>• U/S Doppler studies (umbilical cord and uterine artery)</td>
</tr>
<tr>
<td>Depends on severity:</td>
<td>Maternal hydration with oral or IV fluids to help increase amniotic fluid</td>
</tr>
<tr>
<td>• Mild to moderate cases require no treatment</td>
<td>Vesicoamniotic shunt: if etiology is related to fetal obstructive uropathy; however,</td>
</tr>
<tr>
<td>• If severe, hospitalize and consider therapeutic amniocentesis</td>
<td>pulmonary function may not be restored with restoration of amniotic fluid</td>
</tr>
<tr>
<td></td>
<td>Injection of fluid via amniocentesis will improve condition for ~1 wk – may be</td>
</tr>
<tr>
<td></td>
<td>most helpful for visualizing any associated fetal anomalies</td>
</tr>
<tr>
<td></td>
<td>Consider delivery if term</td>
</tr>
<tr>
<td></td>
<td>Amnio-infusion may be considered during labor via intra-uterine catheter</td>
</tr>
</tbody>
</table>

**Prognosis**

<table>
<thead>
<tr>
<th>Polyhydramnios</th>
<th>Oligohydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-5 fold increase in risk of perinatal mortality</td>
<td>Poorer with early onset</td>
</tr>
<tr>
<td>High mortality related to congenital malformations and pulmonary hypoplasia when diagnosed during T2</td>
<td></td>
</tr>
</tbody>
</table>

---

**Normal Labor and Delivery**

**Definition of Labor**

- **true labor:** regular, painful contractions of increasing intensity associated with progressive dilation and effacement of cervix and descent of presenting part, or progression of station
  - preterm (>20 to <36+6 wk GA)
  - term (37-41+6 wk GA)
  - postterm (>42 wk GA)
- **false labor:** Braxton-Hicks contractions
  - irregular contractions, with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any dilation, effacement, or descent
  - often relieved by rest or sedation

**The Cervix**

- **dilation:** latent phase: 0-3 cm; active phase: 4-10 cm
- **effacement:** thinning of the cervix by percentage or length of cervix (cm)
- **consistency:** firm vs. soft
- **position:** posterior vs. anterior
- **application:** contact between the cervix and presenting part (i.e. well or poorly applied)
- see Bishop score (Table 22, OB35)

**The Fetus**

- **fetal lie**
  - orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, oblique)
- **fetal presentation**
  - fetal part presenting at pelvic outlet
    - breech (complete, frank, footling) (see Figure 9, OB39)
    - cephalic (vertex, face, asynclitic)
    - transverse (shoulder)
    - compound (fetal extremity prolapses along with presenting part)
  - all except vertex are considered malpresentations (see High Risk Labor and Delivery, OB37)
- **fetal position**
  - position of presenting part of the fetus relative to the maternal pelvis
    - OA: most common presentation (“normal”) – left OA most common
    - OP: most rotate spontaneously to OA; may cause prolonged second stage of labor
    - OT: leads to arrest of dilatation
  - normally, fetal head enters maternal pelvis and engages in OT position
  - subsequently rotates to OA position (or OP in a small percentage of cases)
• attitude
  ▪ flexion/extension of fetal head relative to shoulders
  ▪ brow presentation: head partially extended (requires C/S)
  ▪ face presentation: head fully extended
    – mentum posterior always requires C/S, mentum anterior will deliver vaginally

• station
  ▪ position of presenting part relative to ischial spines – determined by vaginal exam
  ▪ at ischial spines = station 0 = engaged
  ▪ -5 to -1 cm above ischial spines or
  ▪ +1 to +5 cm below ischial spines
  ▪ alternatively stations can be placed on a scale from -3 to +3

Figure 7. Fetal positions

Four Stages of Labor

First Stage of Labor
• latent phase
  ▪ uterine contractions typically infrequent and irregular
  ▪ slow cervical dilatation (usually to 3-4 cm) and effacement
• active phase
  ▪ rapid cervical dilatation to full dilatation (nulliparous ~1.2 cm/h, multiparous ~1.5 cm/h)
  ▪ phase of maximum slope on cervical dilatation curve
  ▪ painful, regular contractions q2-3 min, lasting 45-60 s
  ▪ contractions strongest at fundus, weakest at lower segment

Second Stage of Labor
• from full dilatation to delivery of the baby
• mother feels a desire to bear down and push with each contraction
• women may choose a comfortable position that enhances pushing efforts and delivery
  ▪ upright (semi-sitting, squatting) and LLDP are supported in the literature
• progress measured by descent

Third Stage of Labor
• separation and expulsion of the placenta
• can last up to 30 min before intervention indicated
• start oxytocin IV drip, or give 10 U IM or 5 mg IV push after delivery of anterior shoulder in anticipation of placental delivery, otherwise give after delivery of placenta
• routine oxytocin administration in third stage of labor can reduce the risk of PPH by >40%

Signs of Placental Separation
• Gush of blood
• Lengthening of cord
• Uterus becomes globular
• Fundus rises

Continuous Support for Women During Childbirth
Cochrane DB Syst Rev 2011;16:CD003766
Study: Systematic review of 21 RCTs from 11 countries, 15,961 women in labor.
Intervention: Continuous support during labor vs. usual care.
Outcome: Effects on mothers and their babies.
Results: Continuous intrapartum support increased likelihood of shorter labor, spontaneous vaginal birth, decrease in analgesia use, and a decrease in dissatisfaction with childbirth experience. Greatest benefit when provider is not a healthcare professional. Continuous support was also associated with decreased likelihood to have a Cesarean or instrumental vaginal birth, regional anesthesia, or a baby with a low 5 min APGAR score.
Fourth Stage of Labor
- first postpartum hour
- monitor vital signs and bleeding
- repair lacerations
- ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
- inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
- 3rd and 4th stages of labor most dangerous to the mother (i.e. hemorrhage)

The Cardinal Movements of the Fetus During Delivery

Figure 8. Cardinal movements of fetus during delivery
Adapted from illustration in Williams Obstetrics, 19th ed

Analgesic and Anesthetic Techniques in Labor and Birth

- pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

Non-Pharmacologic Pain Relief Techniques
- reduction of painful stimuli
  - maternal movement, position change, counter-pressure, abdominal compression
- activation of peripheral sensory receptors
  - superficial heat and cold
  - immersion in water during labor
  - touch and massage, acupuncture, and acupressure
  - TENS
  - intradermal injection of sterile water
  - aromatherapy
- enhancement of descending inhibitory pathways
  - attention focusing and distraction
  - hypnosis
  - music and audio analgesia
  - biofeedback

Pharmacologic Methods (see Anesthesia, A24)
- nitrous oxide (e.g. self-administered Entonox®)
- narcotics (usually combined with anti-emetic)
- pudendal nerve block
- perineal infiltration with local anesthetic
- regional anesthesis (epidural block, combined spinal-epidural, spinal)
**Fetal Monitoring in Labor**

- see online Fetal Heart Rate Tutorial

**Vaginal Exam**
- membrane status
- cervical effacement (thinning), dilatation, consistency, position, application
- fetal presenting part, position, station
- bony pelvis size and shape
- monitor progress of labor at regular intervals and document in a partogram

**Intrapartum Fetal Monitoring**
- intermittent fetal auscultation with Doppler device q15-30min for 1 min in first stage active phase following a contraction, q5min during second stage when pushing has begun
- continuous electronic FHR monitoring reserved for abnormal auscultation, prolonged labor, and labor which is induced or augmented, meconium present, multiple gestation/fetal complication
  - routine use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate
  - techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
- fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (CTG) to resolve the interpretation of abnormal or atypical patterns

**Electronic FHR Monitoring**
- FHR measured by Doppler; contractions measured by tocometer
- described in terms of baseline FHR, variability (short-term, long-term), and periodicity (accelerations, decelerations)

- **Baseline FHR**
  - normal range is 110-160 bpm
  - parameter of fetal well-being vs. distress

- **Variability**
  - physiologic variability is a normal characteristic of FHR
  - variability is measured over a 15 min period and is described as: absent, minimal (<6 bpm), moderate (6-25 bpm), marked (>25 bpm)
  - normal variability indicates fetal acid-base status is acceptable
  - can only be assessed by electronic fetal monitoring (CTG)
  - variability decreases intermittently even in healthy fetus
  - see Table 19, OB34

- **Periodicity**
  - accelerations: increase of ≥15 bpm lasting ≥15 s, in response to fetal movement or uterine contraction (or ≥10 bpm lasting ≥10 s if <32 wk GA)
  - decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability

<table>
<thead>
<tr>
<th>Table 18. Factors Affecting Fetal Heart Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal Tachycardia (FHR &gt;160)</td>
</tr>
<tr>
<td>Maternal Factors</td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td>Fetal Factors</td>
</tr>
<tr>
<td>Anemia</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Uteroplacental</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

**Fetal Scalp Blood Sampling**
- indicated when atypical or abnormal fetal heart rate is suggested by clinical parameters including heavy meconium or moderately to severely abnormal FHR patterns, including unexplained low variability, repetitive late decelerations, complex variable decelerations, fetal cardiac arrhythmias
  - pH ≥7.25: normal, repeat if abnormal FHR persists
  - pH 7.21-7.24: repeat assessment in 30 min or consider delivery if rapid fall since last sample
  - pH ≤7.20: indicates fetal acidosis, delivery is indicated
• contraindications
  - known or suspected fetal blood dyscrasia (hemophilia, von Willebrand disease)
  - active maternal infection (HIV, genital herpes)

Table 19. Comparison of Decelerations

<table>
<thead>
<tr>
<th>Early Decelerations</th>
<th>Variable Decelerations</th>
<th>Complicated Variable Decelerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Uniform shape with onset early in contraction, returns to baseline by end of contraction, mirrors contraction</td>
<td>• Variable in shape, onset, and duration</td>
<td>• To &lt;70 bpm for &gt;60 s</td>
</tr>
<tr>
<td>• Gradual deceleration</td>
<td>• Most common type of periodicity seen during labor</td>
<td>• Loss of variability or decrease in baseline after deceleration</td>
</tr>
<tr>
<td>• Often repetitive; no effect on baseline FHR or variability</td>
<td>• Often with abrupt drop in FHR; usually no effect on baseline FHR or variability</td>
<td>• Biphasic deceleration</td>
</tr>
<tr>
<td>• Benign, due to vagal response to head compression</td>
<td>• Due to cord compression or, in second stage, forceful pushing with contractions</td>
<td>• Slow return to baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Baseline tachycardia or bradycardia</td>
</tr>
</tbody>
</table>

Table 20. Classification of Intrapartum EFM Tracings

<table>
<thead>
<tr>
<th>Normal Tracing (Category 1)</th>
<th>Atypical Tracing* (Category 2)</th>
<th>Abnormal Tracing* (Category 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>110-160 bpm</td>
<td>Bradycardia 100-110 bpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia &gt; 160 for 30-80 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rising baseline</td>
</tr>
<tr>
<td>Variability</td>
<td>6-25 bpm ≤5 bpm for &lt;40 min</td>
<td>≤5 bpm for 40-80 min</td>
</tr>
<tr>
<td>Decelerations</td>
<td>None</td>
<td>Repetitive (≥3) un-complicated</td>
</tr>
<tr>
<td></td>
<td>Early decelerizations</td>
<td>variable decelerations</td>
</tr>
<tr>
<td></td>
<td>Occasional uncomplicated</td>
<td>Occasional late decelerations</td>
</tr>
<tr>
<td></td>
<td>variable decelerations</td>
<td>Any prolonged deceleration 2-3 min</td>
</tr>
<tr>
<td>Accelerations</td>
<td>Accelerations spontaneous or</td>
<td>Absent with scalp stimulation</td>
</tr>
<tr>
<td></td>
<td>during scalp stimulation</td>
<td>Nearly absent</td>
</tr>
<tr>
<td>Action</td>
<td>EFM may be interrupted for ≤30 min if mother/fetus stable</td>
<td>Further assessment required</td>
</tr>
</tbody>
</table>

Adapted from SOGC Guidelines, September 2008

*Previous classification was “reassuring” vs. “non-reassuring”, but distinction is now made between tracings that have some concerning changes but do not require immediate action (atypical) vs. those with major concerns requiring immediate intervention (abnormal)

Fetal Oxygenation

- uterine contractions during labor decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow and have no adverse effects
- distribution of oxygen to the fetus depends on maternal, uteroplacental, and fetal factors
• fetal response to hypoxia/asphyxia
  ▪ decreased movement, tone, and breathing activities
  ▪ redistribution of fetal blood flow
    ▪ increased flow to brain, heart, and adrenals
    ▪ decreased flow to kidneys, lungs, gut, liver, and peripheral tissues
    ▪ increase in blood pressure
  ▪ transient fetal bradycardia followed by fetal tachycardia
  ▪ anaerobic metabolism (decreased pH)

Table 21. Factors Affecting Fetal Oxygenation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Decreased maternal oxygen carrying</td>
<td>Significant anemia (iron deficiency, hemoglobinopathies,</td>
</tr>
<tr>
<td></td>
<td>capacity</td>
<td>carboxyhemoglobin (smokers)</td>
</tr>
<tr>
<td></td>
<td>Decreased uterine blood flow</td>
<td>Hypotension (blood loss, sepsis), regional anesthesia, maternal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>positioning</td>
</tr>
<tr>
<td></td>
<td>Chronic maternal conditions</td>
<td>Vasculopathies (SLE, type 1 DM, chronic HTN), antiphospholipid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>syndrome, cyanotic heart disease, COPD</td>
</tr>
<tr>
<td>Uteroplacental</td>
<td>Uterine hypertonus</td>
<td>Placental abruption, hyperstimulation secondary to oxytocin, prostaglandins, or normal labor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placental abruption, placental infarction (dysfunction marked by IUGR, oligohydramnios, abnormal Doppler studies), chorioamnionitis, placental edema (DM, hydrops), placental senescence (post-dates)</td>
</tr>
<tr>
<td>Fetal</td>
<td>Cord compression</td>
<td>Oligohydramnios, cord prolapse or entanglement</td>
</tr>
<tr>
<td></td>
<td>Decreased fetal oxygen carrying</td>
<td>Significant anemia (isoimmunization, feto-maternal bleed),</td>
</tr>
<tr>
<td></td>
<td>capacity</td>
<td>carboxyhemoglobin (exposure to smokers)</td>
</tr>
</tbody>
</table>

Induction of Labor

Definition
• artificial initiation of labor before its spontaneous onset for the purpose of delivery of the fetus and placenta

Prerequisites for Labor Induction
• capability for C/S if necessary
• maternal
  ▪ short, thin, soft, anterior cervix with open os (“inducible” or “ripe”)
  ▪ if cervix is not ripe, use prostaglandin vaginal insert (Cervidil®), prostaglandin gel (Prepidil®), or Foley catheter
• fetal
  ▪ normal fetal heart tracing
  ▪ cephalic presentation
  ▪ adequate fetal monitoring available
• likelihood of success determined by Bishop score
  ▪ cervix considered unfavorable if <6
  ▪ cervix favorable if ≥6
  ▪ score of 9-13 associated with high likelihood of vaginal delivery

Table 22. Bishop Score

<table>
<thead>
<tr>
<th>Cervical Characteristic</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position</td>
<td>Posterior</td>
<td>Mid</td>
<td>Anterior</td>
<td>–</td>
</tr>
<tr>
<td>Consistency</td>
<td>Firm</td>
<td>Medium</td>
<td>Soft</td>
<td>–</td>
</tr>
<tr>
<td>Effacement (%)</td>
<td>0-20</td>
<td>20-50</td>
<td>50-70</td>
<td>≥50</td>
</tr>
<tr>
<td>Dilatation (cm)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
<td>≥5</td>
</tr>
<tr>
<td>Station of Fetal Head</td>
<td>-3</td>
<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

Indications
• post-dates pregnancy (generally >41 wk) = most common reason for induction
• maternal factors
  ▪ DM = second most common reason for induction
  ▪ gestational HTN
  ▪ other maternal medical problems, e.g. renal or lung disease
• maternal-fetal factors
  ▪ isoimmunization, PROM, chorioamnionitis, post-term pregnancy

Induction vs. Augmentation
Induction is the artificial initiation of labor
Augmentation promotes contractions when spontaneous contractions are inadequate

Induction is indicated when the risk of continuing pregnancy exceeds the risks associated with induced labor and delivery

Consider the Following Before Induction
• Indication for induction
• Contraindications
• GA
• Cervical favorability
• Fetal presentation
• Potential for CPD
• Fetal well-being/FHR
• Membrane status
• fetal factors
  ▪ suspected fetal jeopardy as evidenced by biochemical or biophysical indications
  ▪ fetal demise, IUGR

Risks
• failure to achieve labor and/or vaginal birth
• uterine hyperstimulation and fetal compromise
• maternal side effects to medications
• uterine atony and PPH
• uterine rupture

Contraindications
• maternal
  ▪ prior classical or inverted T-incision or uterine surgery (e.g. myomectomy)
  ▪ unstable maternal condition
  ▪ active maternal genital herpes
  ▪ invasive cervical carcinoma
  ▪ pelvic structure deformities
• maternal-fetal
  ▪ placenta previa or vasa previa
  ▪ cord presentation
• fetal
  ▪ fetal distress, malpresentation, preterm fetus without lung maturity

Induction Methods

CERVICAL RIPENING

Definition
• use of medications or other means to soften, efface, and dilate the cervix to increase likelihood of induction success
• ripening of an unfavorable cervix (Bishop score <6) is warranted prior to induction of labor

Methods
• intravaginal prostaglandin PGE2 gel (Prostin® gel): long and closed cervix
  ▪ recommended dosing interval of prostaglandin gel is every 6 to 12 h up to 3 doses
• intravaginal PGE2 (Cervidil®): long and closed cervix, may use if ROM
  ▪ continuous release, can be removed if needed
  ▪ controlled release PGE2
• Foley catheter placement to mechanically dilate the cervix

INDUCTION OF LABOR

Amniotomy
• artificial rupture of membranes (amniotomy) to stimulate prostaglandin synthesis and secretion; may try this as initial measure if cervix is dilated
• few studies address the value of amniotomy alone for induction of labor
• amniotomy plus intravenous oxytocin: more women delivered vaginally at 24 h than amniotomy alone (relative risk = 0.03) and had fewer instrumental vaginal deliveries (relative risk = 5.5)

Oxytocin
• oxytocin (Pitocin®): 10 U in 1L NS, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60min to a max of 36-48 mU/min
  ▪ reduces rate of unsuccessful vaginal deliveries within 24 h when used alone (8.3% vs. 54%, RR 0.16)
  ▪ ideal dosing regime of oxytocin is not known
  ▪ current recommendations: use the minimum dose to achieve active labor and increase q30min as needed
  ▪ reassessment should occur once a dose of 20 mU/min is reached
• potential complications
  ▪ hyperstimulation/tetanic contraction (may cause fetal distress or rupture of uterus)
  ▪ uterine muscle fatigue, uterine atony (may result in PPH)
  ▪ vasopressin-like action causing anti-diuresis

Augmentation of Labor
• augmentation of labor is used to promote adequate contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur
• oxytocin (0.5-2 mU/min IV increasing by 1-2 mU/min q20-60min to a max of 36-48 mU/min)
**Preterm Labor**

**Definition**
- labor occurring between 20 and 37 wk gestation

**Etiology**
- idiopathic (most common)
- maternal: infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), genital infection (bacterial vaginosis is associated with a 2-fold increase in relative risk of preterm birth), HTN, DM, chronic illness, mechanical factors, previous obstetric, gynecological, and abdominal surgeries, socio-environmental (poor nutrition, smoking, drugs, alcohol, stress)
- maternal-fetal: PPROM (common), polyhydramnios, placenta previa, placental abortion, or placental insufficiency
- fetal: multiple gestation, congenital abnormalities of fetus, fetal hydrops
- uterine: incompetent cervix, excessive enlargement (hydramnios), malformations (leiomyomas, septate uterus)

**Epidemiology**
- preterm labor complicates about 10% of pregnancies

**Risk Factors and Prediction of PTL**
- maternal risk scoring using above etiologies fails to identify up to 70% of preterm deliveries and is therefore of limited use
- prior history of spontaneous PTL: most important risk factor
- prior history cervical excisions or mechanical dilatation
- cervical length: measured by transvaginal U/S (cervical length >30 mm has high negative predictive value for PTL before 34 wk)
- identification of bacterial vaginosis (Rx metronidazole) and ureaplasma urealyticum (Rx erythromycin) infections: routine screening not supported by current data but it is reasonable to screen high risk women
- fetal fibronectin: a glycoprotein in amniotic fluid and placental tissue functioning to maintain integrity of chorionic-decidual interface in asymptomatic women
  - positive if >50 ng/mL
  - in symptomatic women (i.e. preterm contractions), fetal fibronectin is most effectively combined with U/S detecting cervical length
  - if cervical length is not short and fetal fibronectin is negative, preterm labor is highly unlikely

**Clinical Features**
- regular contractions (2 in 10 min)
- cervix >2 cm dilated, 80% effaced, or documented change in cervix

**Management**

**A. Initial**
- transfer to appropriate facility if stable
- hydration (NS at 150 mL/h)
- bed rest in LLDP
- sedation (morphine)
- avoid repeated pelvic exams (increased infection risk)
- U/S examination of fetus (GA, BPP, position, placenta location, estimated fetal weight)
- prophylactic antibiotics; controversial but may help delay delivery, important to consider if PPROM

**B. Suppression of Labor – Tocolysis**
- does not inhibit preterm labor completely, but may buy time (used for <48 h) to allow for betamethasone valerate (Celestone®) and/or transfer to appropriate center for care of the premature infant
- requirements (all must be satisfied)
  - preterm labor
  - live, immature fetus, intact membranes, cervical dilatation of <4 cm
  - absence of maternal or fetal contraindications
- contraindications
  - maternal: bleeding (placenta previa or-abortion), maternal disease (HTN, DM, heart disease), preeclampsia or eclampsia, chorioamnionitis
  - fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)

**Tocolytics for Preterm Premature Rupture of Membranes**
*Cochrane DB Syst Rev 2014;2:CD007062*

**Purpose:** To assess the potential benefits and harms of tocolysis in women with PPROM.

**Selection Criteria:** Pregnant women with singleton pregnancies and PPROM (23-36 wk and 6 d GA).

**Results:** 8 studies with 408 women total.
- Prophylactic tocolysis with PPROM was associated with increased overall latency, without additional benefits for maternal/neonatal outcomes. For women with PPROM before 34 wk, there was a significantly increased risk of chorioamnionitis in women who received tocolysis. Neonatal outcomes were not significantly different.

**Conclusion:** Although there are limitations to the studies, there is currently insufficient evidence to support tocolytic therapy for women with PPROM, as there was an increase in maternal chorioamnionitis with no significant benefits to the infant.
• agents
  ▪ calcium channel blockers: Nifedipine
    • 20 mg PO loading dose followed by 20 mg PO 90 min later
    • 20 mg can be continued q3-8h for 72 h or to a max of 180 mg
    • 10 mg PO q20min x 4 doses
  ▪ prostaglandin synthesis inhibitors: Indomethacin
    • 1st line for early preterm labor (<30 wk GA) or polyhydramnios
    • 50-100 mg PO loading dose followed by 25 mg q4-6h
    • magnesium sulphate was previously used for tocolysis; currently, its primary use in obstetrics is limited to neuroprotection or prevention of eclampsia

C. Enhancement of Fetal Pulmonary Maturity
• betamethasone valerate (Celestone®) 12 mg IM q24h x 2 doses or dexamethasone 6 mg IM q12h x 4 doses
  ▪ 28-34 wk GA: reduces incidence of RDS
  ▪ 24-28 wk GA: reduces severity of RDS, overall mortality, and rate of IVH
  ▪ specific maternal contraindications: active TB

D. Cervical Cerclage
• definition: placement of cervical sutures at the level of the internal os, usually at the end of the first trimester and removed in the third trimester
• indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
  ▪ emerging evidence indicates that progesterone suppositories are superior to cerclage in preventing preterm labor late in pregnancy
• diagnosis of cervical incompetence
  ▪ obstetrical Hx: silent cervical dilation
  ▪ ability of cervix to hold an inflated Foley catheter during a hysterosonogram
• proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. conization of the cervix, connective tissue disorders)

Prognosis
• preterm is the leading cause of perinatal morbidity and mortality
• 30 wk or 1,500 g (3.3 lb) = 90% survival
• 33 wk or 2,000 g (4.4 lb) = 99% survival

Prevention of Preterm Labor
• preventative measures: good prenatal care, identify pregnancies at risk, treat silent vaginal infection or UTI, patient education
• transvaginal ultrasound of cervical length is recommended only for high-risk pregnancies

**Premature Rupture of Membranes**

**Definitions**
• PROM or amniorrhea: rupture of membranes prior to labor at any GA
• prolonged ROM: >24 h elapsed between rupture of membranes and onset of labor
• PPROM: rupture of membranes before 37 wk AND prior to onset of labor

**Risk Factors**
• maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STD, UTI), family history of PROM, low socioeconomic class/poor nutrition
• fetal: congenital anomaly, multiple gestation
• other risk factors associated with PTL

**Clinical Features**
• history of fluid gush or continued leakage

** Investigations**
• sterile speculum exam (avoid introduction of infection)
  ▪ pooling of fluid in the posterior fornix
  ▪ may observe fluid leaking out of cervix on cough/Valsalva (“cascade”)
• nitrazine (amniotic fluid turns nitrazine paper blue)
  ▪ low specificity as can be positive with blood, urine, or semen
• ferning (high salt in amniotic fluid evaporates, looks like ferns under microscope)
• U/S to rule out fetal anomalies, assess GA, and BPP

**Membrane Status Determined by**
• pooling of fluid on speculum exam
• increased pH of vaginal fluid (nitrazine test)
• ferning of fluid under light microscopy
• decreased AFV on U/S

**L/S Ratio (Lecithin:Sphingomyelin Ratio)**
Lecithin levels increase rapidly after 35 wk gestation, whereas sphingomyelin levels remain relatively constant. The L/S ratio is a measure of fetal lung maturity – less than 2:1 indicates pulmonary immaturity. Presence of blood or meconium in the amniotic fluid can affect the ratio

**Cerclage for Short Cervix on Ultrasonography in Women With Singleton Gestations and Previous Preterm Birth**
*Obstet Gynecol* 2011;117:663-671

**Purpose**
To determine if cerclage prevents preterm birth (≤35 wk gestation) and perinatal mortality and morbidity among women with previous spontaneous preterm birth, asymptomatic singleton gestation, and short cervical length (<25 mm before 24 wk gestation) on transvaginal ultrasonography.

**Methods**
Meta-analysis of randomized trials identified using searches on MEDLINE, PUBMED, EMBASE, and the Cochrane Library.

**Results**
5 trials included. Preterm birth was significantly lower among women receiving cerclage vs. those not (RR=0.70, 95% CI 0.55-0.89). Cerclage also significantly reduced preterm birth before 24, 28, 32, and 37 wk gestation.

Perinatal mortality and morbidity were significantly lower in the cerclage group (RR=0.64, 95% CI 0.45-0.91).

**Conclusions**
Cerclage significantly prevents preterm birth and perinatal mortality and morbidity in the specific group of women.
Management
- admit for expectant management and monitor vitals q4h, daily BPP and WBC count
- avoid introducing infection with examinations (do NOT do a bimanual exam)
- cultures (cervix for GC, lower vagina for GBS)
- assess fetal lung maturity by L/S ratio of amniotic fluid
  - consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <32 wk and no evidence of infection
  - consider tocolysis for 48 h to permit administration of steroids if PPROM induces labor
- if not in labor or labor not indicated, consider antibiotics (controversial)
  - studies show broad spectrum coverage increases the time to onset of labor from PROM by 5-7 d with no increase in maternal or neonatal morbidity or mortality
- deliver urgently if evidence of fetal distress and/or chorioamnionitis

Table 23. PROM Management

<table>
<thead>
<tr>
<th>Degree of Prematurity</th>
<th>Management</th>
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<tbody>
<tr>
<td>&lt;24 wk</td>
<td>Consider termination (poor outcome due to pulmonary hypoplasia)</td>
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<tr>
<td>24-25 wk</td>
<td>Individual consideration with counseling of parents re: risks to preterm infants</td>
</tr>
<tr>
<td>26-34 wk</td>
<td>Expectant management as prematurity complications are significant</td>
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<tr>
<td>34-36 wk</td>
<td>“Gray zone” where risk of death from RDS and neonatal sepsis is the same</td>
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<tr>
<td>≥37 wk</td>
<td>Induction of labor since the risk of death from sepsis is greater than RDS</td>
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</table>

Prognosis
- varies with gestational age
- 90% of women with PROM at 28-34 wk GA go into spontaneous labor within 1 wk
- 50% of women with PROM at <26 wk GA go into spontaneous labor within 1 wk
- complications: cord prolapse, intrauterine infection (chorioamnionitis), premature delivery, limb contracture

Breech Presentation

Definition
- fetal buttocks or lower extremity is the presenting part as determined on U/S
- complete (10%): flexion at hips and knees
- frank (60%): flexion at hips, extension at knees
  - most common type of breech presentation
  - most common breech presentation to be delivered vaginally
- footling (30%): may be single or double with extension at hip(s) and knee(s) so that foot is the presenting part

Epidemiology
- occurs in 3-4% of pregnancies at term (25% before 28 wk)

Risk Factors
- maternal: pelvis (contracted), uterus (shape abnormalities, intrauterine tumors, fibroids), extraterine tumors causing compression, grand multiparity
- maternal-fetal: placenta (previa), amniotic fluid (poly-/oligohydramnios)
- fetal: prematurity, multiple gestation, congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations), abnormalities in fetal tone and movement, aneuploidy

Management
- ECV: repositioning of fetus within uterus under U/S guidance
  - overall success rate of 65%
  - criteria: singleton, unengaged presenting part, reactive NST
  - contraindications: previous T3 bleed, prior classical C/S, previous myomectomy, oligohydramnios, PROM, placenta previa, abnormal U/S, suspected IUGR, HTN, uteroplacental insufficiency, nuchal cord
  - risks: abruption, cord compression
  - method: tocometry, followed by ultrasound guided transabdominal manipulation of fetus with consistent fetal heart monitoring
  - if patient Rh negative, give Rhogam® prior to procedure
  - good prognostic factors (for a successful version)
    - multiparous, good fluid volume, small baby, skilled obstetrician
    - pre- or early labor ultrasound to assess type of breech presentation, fetal growth, estimated weight, attitude of fetal head; if ultrasound unavailable, recommend C/S
  - trial of labor and elective C/S should be presented as options with the risks and benefits outlined; obtain informed consent

Criteria for Vaginal Breech Delivery
- Frank or complete breech, GA >36 wk
- EFW 2,500-3,800 g based on clinical and U/S assessment (5.5–8.5 lb)
- Fetal head flexed
- Continuous fetal monitoring
- 2 experienced obstetricians, assistant, and anesthetist present
- Ability to perform emergency C/S within 30 min if required
• method for vaginal breech delivery
  ▪ encourage effective maternal pushing efforts
  ▪ at delivery of after-coming head, assistant must apply suprapubic pressure to flex and engage fetal head
  ▪ delivery can be spontaneous or assisted; avoid fetal traction
  ▪ apply fetal manipulation only after spontaneous delivery to level of umbilicus
• C/S recommended if: the breech has not descended to the perineum in the second stage of labor after 2 h, in the absence of active pushing, or if vaginal delivery is not imminent after 1 h of active pushing
• contraindications to vaginal breech delivery
  ▪ cord presentation
  ▪ clinically inadequate maternal pelvis
  ▪ fetal factors incompatible with vaginal delivery

Prognosis
regardless of route of delivery, breech infants have lower birth weights and higher rates of perinatal mortality, congenital anomalies, abruption, and cord prolapse

Vaginal Birth After Cesarean
(Trial of Labor After Cesarean)
• recommended after previous low transverse incision
• success rate varies with indication for previous C/S (generally 60-80%)
• risk of uterine rupture (<1% with low transverse incision)

Contraindications
• previous classical, inverted T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
• history of hysteroscopy or previous uterine rupture
• multiple gestation
• non-vertex presentation or placenta previa
• inadequate facilities or personnel for emergency C/S

Prolonged Pregnancy

Definition
• pregnancy beyond 42 wk GA

Epidemiology
• 41 wk GA: up to 27%
• 42 wk GA: 4-14%

Etiology
• most cases idiopathic
• anencephalic fetus with no pituitary gland
• placental sulfatase deficiency (X-linked recessive condition in 1/2,000-1/6,000 infants) – rare

Clinical Features
• postmaturity syndrome: 10-20% of post-term pregnancies (fetal weight loss, reduction in subcutaneous fat, scaling, dry skin from placental insufficiency, long thin body, open-eyed, alert and worried look, long nails, palms and soles wrinkled)
• with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental aging and infarction, macrosomia, dystocia, fetal distress, operative deliveries

Management
• GA 40-41 wk: expectant management
  ▪ no evidence to support IOL or C/S unless other risk factors for morbidity are present (see prognosis)
• GA >41 wk: offer IOL if vaginal delivery is not contraindicated
  ▪ IOL shown to decrease C/S, fetal heart rate changes, meconium staining, macrosomia, and death when compared with expectant management
• GA >41 wk and expectant management elected: serial fetal surveillance
  ▪ fetal movement count by the mother
  ▪ BPP q3-4d
  ▪ If AFI is decreased, labor will be induced
Intrauterine Fetal Death

Definition
• fetal death in utero after 20 wk GA

Epidemiology
• 1% of pregnancies

Etiology
• 50% idiopathic
• 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, APS

Clinical Features
• decreased perception of fetal movement by mother
• SFH and maternal weight not increasing
• absent fetal heart tones (not diagnostic)
• high MSAFP

Management
• diagnosis: absent cardiac activity and fetal movement on U/S required for diagnosis
• determine secondary cause
  ▪ maternal: Hba1c, Kleihauer-Betke, VDRL, ANA, antibody screens, INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, TORCH screen
  ▪ fetal: chromosomes, cord blood, skin biopsy, genetics evaluation, autopsy
  ▪ placenta: pathology, bacterial cultures

DIC: Generalized Coagulation and Fibrinolysis Leading to Depletion of Coagulation Factors

Obstetrical Causes
• Abruption
• Gestational HTN
• Fetal demise
• PPH

DIC-specific Blood Work
• Platelets
• aPTT and PT
• FDP
• Fibrinogen

Treatment
• Treat underlying cause
• Supportive
  • Fluids
  • Blood products
  • FFP, platelets, cryoprecipitate
• Consider anti-coagulation as VTE prophylaxis

Complications of Labor and Delivery

Meconium in Amniotic Fluid

Epidemiology
• present early in labor in 10% of pregnancies
• in general, meconium may be present in up to 25% of all labors; usually NOT associated with poor outcome, but extra care is required at time of delivery to avoid aspiration

Etiology
• likely cord compression ± uterine hypertonus
• may indicate undiagnosed breech
• increasing meconium during labor may be a sign of fetal distress

Features
• consistency and color
  ▪ light yellow/green or dark green-black in color
  ▪ may be watery or thicker

Treatment
• call respiratory therapy, neonatology, or pediatrics to delivery room
• oropharynx suctioning upon head expulsion or immediately after delivery if baby not breathing spontaneously (do NOT stimulate infant before)
• consider amnioinfusion of ~800 mL of IV NS over 50-80 min during active stage of labor and a maintenance dose of ~3 mL/min until delivery
• closely monitor FHR for signs of fetal distress
**Abnormal Progression of Labor (Dystocia)**

**Definition**
- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labor
- during active phase: >4 h of <0.5 cm/h
- during 2nd phase: >1 h with no descent during active pushing

**Etiology**
- **Power** (leading cause): contractions (hypotonic, incoordinate), inadequate maternal expulsive efforts
- **Passenger**: fetal position, attitude, size, anomalies (hydrocephalus)
- **Passage**: pelvic structure (CPD), maternal soft tissue factors (tumors, full bladder or rectum, vaginal septum)
- **Psyche**: hormones released in response to stress may contribute to dystocia; psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed

**Management**
- confirm diagnosis of labor (rule out false labor)
- search for factors of CPD
- diagnosed if adequate contractions measured by intrauterine pressure catheter (IUPC) with no descent/dilatation for >2 h
- management: if CPD ruled out, IV oxytocin augmentation ± amniotomy

**Risks of Dystocia**
- inadequate progression of labor is associated with an increased incidence of:
  - maternal stress
  - maternal infection
  - postpartum hemorrhage
  - need for neonatal resuscitation

**Shoulder Dystocia**

**Definition**
- impaction of anterior shoulder of fetus against symphysis pubis after fetal head has been delivered
- life threatening emergency

**Etiology/Epidemiology**
- incidence 0.15-1.4% of deliveries
- occurs when breadth of shoulders is greater than biparietal diameter of the head

**Risk Factors**
- maternal: obesity, DM, multiparity
- fetal: prolonged gestation, macrosomia
- labor
  - prolonged 2nd stage
  - instrumental midpelvic delivery

**Clinical Features**
- “turtle sign”: head delivered but retracts against inferior portion of pubic symphysis
  - complications
    - chest compression by vagina or cord compression by pelvis can lead to hypoxia
    - brachial plexus injury (Erb’s palsy: C5-C7; Klumpke’s palsy: C8-T1)
      - 90% resolve within 6 mo
    - fetal fracture (clavicle, humerus, cervical spine)
    - maternal perineal injury, may result in PPH

**Treatment**
- goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved
- other options
  - cleidotomy (deliberate fracture of neonatal clavicle)
  - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent C/S
  - symphysiotomy

**Prognosis**
- 1% risk of long-term disability for infant
**Umbilical Cord Prolapse**

**Definition**
- descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

**Etiology/Epidemiology**
- increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, CPD
- incidence: 0.17-0.63%

**Clinical Features**
- visible or palpable cord
- FHR changes (variable decelerations, bradycardia, or both)

**Treatment**
- emergency C/S
- O₂ to mother, monitor fetal heart
- alleviate pressure of the presenting part on the cord by placing digit in vagina (maintain this position until C/S)
- keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
- position mother in Trendelenburg or knee-to-chest position
- if fetal demise or too premature (<22 wk), allow labor and delivery

**Uterine Rupture**

**Etiology/Epidemiology**
- associated with previous uterine scar (in 40% of cases), hyperstimulation with oxytocin, grand multiparity, and previous intrauterine manipulation
- generally occurs during labor, but can occur earlier with a classical incision
- 0.5-0.8% incidence, up to 12% with classical incision

**Clinical Features**
- prolonged fetal bradycardia – most common presentation
- acute onset abdominal pain
- hyper or hypotonic uterine contractions
- vaginal bleed

**Risk Factors**
- uterine scarring (i.e. previous uterine surgeries including Cesarean, perforation with D&C)
- excessive uterine stimulation (i.e. protracted labor, oxytocin)
- uterine trauma (i.e. operative equipment, ECV)
- multiparity
- uterine abnormalities

**Treatment**
- rule out placental abruption
- immediate delivery for fetal survival
- maternal stabilization (may require hysterectomy)

**Complications**
- maternal mortality 1-10%
- maternal hemorrhage, shock, DIC
- amniotic fluid embolus
- hysterectomy if uncontrollable hemorrhage
- fetal distress, associated with 50% fetal mortality

**Approach to the Management of Shoulder Dystocia**

**ALARMER**
- Apply suprapubic pressure and ask for help
- Legs in full flexion (McRoberts’s maneuver)
- Anterior shoulder disimpaction (suprapubic pressure)
- Release posterior shoulder by rotating it anteriorly with hand in the vagina under adequate anesthesia
- Manual corkscrew i.e. rotate the fetus by the posterior shoulder until the anterior shoulder emerges from behind the maternal symphysis
- Evisceration
- Rollover (on hands and knees)

*Note that suprapubic pressure and McRoberts’s maneuver together will resolve 90% of cases

**Umbilical Cord Accident Causes**
- Nuchal cord
- Type A (looped)
- Type B (hitched)
- Body loop
- Single artery
- True knot
- Torsion
- Velamentous
- Short cord <35 cm
- Long cord >80 cm

**Maternal Mortality Causes**
- Thromboembolism
- Cardiac event
- Suicide
- Sepsis
- Ectopic pregnancy
- HTN
- Amniotic fluid embolism
- Hemorrhage
**Amniotic Fluid Embolus**

**Definition**
- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

**Etiology/Epidemiology**
- rare intrapartum or immediate postpartum complication
- 60-80% maternal mortality rate, accounts for 10% of all maternal deaths
- leading cause of maternal death in induced abortions and miscarriages
- 1/8,000-1/80,000 births

**Risk Factors**
- placental abruption
- rapid labor
- multiparity
- uterine rupture
- uterine manipulation

**Differential Diagnosis**
- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruption, chronic coagulopathy

**Clinical Features**
- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia), and coagulopathy
- seizure in 10%
- ARDS and left ventricular dysfunction seen in survivors

**Management**
- supportive measures (high flow O₂, ventilation support, fluid resuscitation, inotropic support, ± intubation), coagulopathy correction
- ICU admission

**Chorioamnionitis**

**Definition**
- infection of the chorion, amnion, and amniotic fluid typically due to ascending infection by organisms of normal vaginal flora

**Etiology/Epidemiology**
- incidence 1-5% of term pregnancies and up to 25% in preterm deliveries
- ascending from vagina
- predominant microorganisms include: GBS, Bacteroides and Prevotella species, E. coli, and anaerobic Streptococcus

**Risk Factors**
- prolonged ROM, long labor, multiple vaginal exams during labor, internal monitoring
- bacterial vaginosis and other vaginal infections

**Clinical Features**
- maternal fever, maternal or fetal tachycardia, uterine tenderness, foul and purulent cervical discharge

**Investigations**
- CBC: leukocytosis
- amniotic fluid: leukocytes or bacteria

**Treatment**
- IV antibiotics
  - ampicillin (2 g IV q6h) and gentamicin (1.5 mg/kg q8h)
  - anaerobic coverage (i.e. clindamycin if C/S)
- expedient delivery regardless of gestational age

**Complications**
- bacteremia of mother or fetus, wound infection if C/S, pelvic abscess, infant meningitis

**Clinical Features of Chorioamnionitis**
- Temperature
- Tachycardia (maternal or fetal)
- Tenderness (uterine)
- Foul discharge
Operative Obstetrics

Operative Vaginal Delivery

Definition
- forceps or vacuum extraction

Indications
- fetal
  - atypical or abnormal fetal heart rate tracing
  - consider if second stage is prolonged as this may be due to poor contractions or failure of fetal head to rotate
- maternal
  - need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
  - exhaustion, lack of cooperation, and excessive analgesia may impair pushing effort

Forceps

Outlet Forceps Position
- head visible between labia in between contractions
- sagittal suture in or close to AP diameter
- rotation cannot exceed 45°

Low Forceps Position
- presenting part at station +2 or greater
- subdivided based on whether rotation less than or greater than 45 degrees

Mid Forceps Position
- presenting part below spines but above station +2
- rarely done

Types of Forceps
- Simpson or Tucker-McLane forceps for OA presentations
- Kielland (rotational) forceps when rotation of head required
- Piper forceps for breech

Vacuum Extraction

- traction instrument used as alternative to forceps delivery; aids maternal pushing

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<thead>
<tr>
<th>Table 24. Advantages and Disadvantages of Forceps vs. Vacuum Extraction</th>
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<tr>
<td><strong>Forces</strong></td>
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<tr>
<td>Advantages</td>
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<td>Complications</td>
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Lacerations

- first degree: involves skin and vaginal mucosa but not underlying fascia and muscle
- second degree: involves fascia and muscles of the perineal body but not the anal sphincter
- third degree: involves the anal sphincter but does not extend through it
- fourth degree: extends through the anal sphincter into the rectal mucosa
### Episiotomy

**Definition**
- incision in the perineal body at the time of delivery
- essentially a controlled second degree laceration
- midline: incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernousus muscle
  - better healing but increased risk of deep tear
- mediolateral: incision through bulbocavernousus, superficial transverse perineal muscle, and levator ani
  - reduced risk of extensive tear but poorer healing and more pain
  - easier to repair

**Indications**
- to relieve obstruction of the unyielding perineum
- instrumental delivery
- controversial between practitioners as to whether it is preferable to make a cut or let the perineum tear as needed
- current evidence suggests letting perineum tear and then repair as needed (restricted use)

**Complications**
- infection, hematoma, extension into anal musculature, or rectal mucosa, fistula formation, incontinence

### Cesarean Delivery

**Epidemiology**
- incidence 20-25%

**Indications**
- maternal: obstruction, active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery, underlying maternal illness (eclampsia, HELLP syndrome, heart disease)
- maternal-fetal: failure to progress, placental abruption or previa, vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, certain congenital anomalies

**Types of Cesarean Incisions**
- skin
  - transverse (i.e. Pfannenstiel)
    - decreased exposure and slower entry
    - improved strength and cosmesis
  - vertical midline
    - rapid peritoneal entry and increased exposure
    - increased dehiscence
- uterine
  - low transverse (most common): in noncontractile segment
    - decreased chance for rupture in subsequent pregnancies
  - low vertical
    - used for very preterm infants, poorly developed maternal lower uterine segment
    - classical (rare): in thick, contractile segment
    - used for transverse lie, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid, morbidly obese patients

**Risks/Complications**
- anesthesia
- hemorrhage (average blood loss ~1,000 cc)
- infection (UTI, wound, endometritis)
- single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g)
- injury to surrounding structures (bowel, bladder, ureter, uterus)
- thromboembolism
- increased recovery time/hospital stay
- maternal mortality (<0.1%)
Puerperal Complications

- puerperium: 6 wk period of adjustment after pregnancy when pregnancy-induced anatomic and physiologic changes are reversed

Postpartum Hemorrhage

Definition
- loss of >500 mL of blood at the time of vaginal delivery, or >1,000 mL with C/S
- early – within first 24 h postpartum
- late – after 24 h but within first 6 wk

Epidemiology
- incidence 5-15%

Etiology (4 Ts)
1. Tone
   - uterine atony
     - most common cause of PPH
     - avoid by giving oxytocin with delivery of the anterior shoulder or placenta
     - occurs within first 24 h
     - due to
       - labor (prolonged, precipitous, induced, augmented)
       - uterus (infection, over-distention)
       - placenta (abruption, previa)
       - maternal factors (grand multiparity, gestational HTN)
       - halothane anesthesia
2. Tissue
   - retained placental products
   - retained blood clots in an atonic uterus
   - gestational trophoblastic neoplasia
3. Trauma
   - laceration (vagina, cervix, uterus), episiotomy, hematoma (vaginal, vulvar, retroperitoneal), uterine rupture, uterine inversion
4. Thrombin
   - coagulopathy
     - most identified prior to delivery (low platelets increases risk)
     - includes hemophilia, DIC, Aspirin® use, ITP, TTP, vWD (most common)
     - therapeutic anti-coagulation

Investigations
- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of tone, tissue, or trauma
- may be helpful to observe red-topped tube of blood – no clot in 7-10 min indicates coagulation problem

Management
- ABCs
- 2 large bore IVs and crystalloids
- CBC, coagulation profile, cross and type 4 units pRBCs
- treat underlying cause

Medical Therapy
- oxytocin 20 U/L NS or RL IV continuous infusion
  - in addition can give 10 U IMM after delivery of the placenta
- methylergonovine maleate (ergotamine) 0.25 mg IM/IMM q5min up to 1.25 mg; can be given as IV bolus of 0.125 mg (may exacerbate HTN)
- carboprost (Hemabate®), a synthetic PGF-1α analog 0.25 mg IM/IMM q15min to max 2 mg
  (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary, renal, and hepatic dysfunction)
- misoprostol 600 µg-1 g (side effect: pyrexia)
- tranexamic acid (Cyklokapron®) 1 g IV, an antifibrinolytic
Local Control
- bimanual compression: elevate the uterus and massage through patient's abdomen
- uterine packing (mesh with antibiotic treatment)
- Bakri Balloon for tamponade: may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR

Surgical Therapy (Intractable PPH)
- D&C (beware of vigorous scraping which can lead to Asherman's syndrome)
- embolization of uterine artery or internal iliac artery by interventional radiologist
- laparotomy with bilateral ligation of uterine artery (may be effective), internal iliac artery (not proven), ovarian artery, or hypogastric artery
- hysterectomy last option with angiographic embolization if post-hysterectomy bleeding

Retained Placenta

Definition
- placenta undelivered after 30 min postpartum

Etiology
- placenta separated but not delivered
- abnormal placental implantation (placenta accreta, placenta increta, placenta percreta)

Risk Factors
- placenta previa, prior C/S, post-pregnancy curettage, prior manual placental removal, uterine infection

Clinical Features
- incomplete placenta removed
- risk of postpartum hemorrhage and infection

Investigations
- explore uterus
- assess degree of blood loss

Management
- 2 large bore IVs, type and screen
- Brant maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL NS into umbilical vein
- manual removal if above fails
- D&C if required

Uterine Inversion

Definition
- inversion of the uterus through cervix ± vaginal introitus

Etiology/Epidemiology
- often iatrogenic (excess cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous (lax uterine ligaments)
- 1/1,500-1/2,000 deliveries

Clinical Features
- can cause profound vasovagal response with vasodilation and hypovolemic shock
- shock may be disproportionate to maternal blood loss

Management
- urgent management essential, call anesthesia
- ABCs: initiate IV crystalloids
- can use tocolytic drug (see Management of Preterm Labor, OB37) or nitroglycerin IV to relax uterus and aid replacement
- replace uterus without removing placenta
- remove placenta manually and withdraw slowly
- IV oxytocin infusion (only after uterus replaced)
- re-explore uterus
- may require general anesthetic ± laparotomy
**Postpartum Pyrexia**

**Definition**
- fever >100.4°F on any 2 of the first 10 d postpartum, except the first day

**Etiology**
- endometritis
- wound infection secondary to C/S
- mastitis/engorgement
- UTI
- atelectasis
- pneumonia

Investigations
- detailed history and physical exam, relevant cultures
- for endometritis: blood and genital cultures

**Treatment**
- depends on etiology
  - infection: empiric antibiotics, adjust when sensitivities available
  - endometritis: clindamycin + gentamycin IV
  - mastitis: cephalexin (if pen-allergic)
  - wound infection: cephalexin
  - DVT: anticoagulants
- prophylaxis against post-C/S endometritis: begin antibiotic immediately after cord clamping and administer only 1-3 doses – cefazolin is most common choice

**ENDOMETRITIS**
- definition: infection of uterine myometrium and parametrium
- clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling discharge, or lochia
- treatment: depends on infection severity; oral antibiotics if well, IV with hospitalization in moderate to severe cases

**VENOUS THROMBOEMBOLISM**
- see *Venous Thromboembolism, OB20*

**Mastitis**
- definition: inflammation of mammary glands
- must rule out inflammatory carcinoma, as indicated
- differentiate from mammary duct ectasia: mammary duct(s) beneath nipple clogged and dilated ± ductal inflammation ± nipple discharge (thick, gray to green), often postmenopausal women

**Table 25. Lactational vs. Non-Lactational Mastitis**

<table>
<thead>
<tr>
<th></th>
<th>Lactational</th>
<th>Non-Lactational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>More common than non-lactational</td>
<td>Periductal mastitis most common</td>
</tr>
<tr>
<td></td>
<td>Often 2-3 wk postpartum</td>
<td>Mean age 32 yr</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td><em>S. aureus</em></td>
<td>May be sterile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be infected with <em>S. aureus</em> or other anaerobes</td>
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<tr>
<td></td>
<td></td>
<td>Smoking is risk factor</td>
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<tr>
<td></td>
<td></td>
<td>May be associated with mammary duct ectasia</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Unilateral localized pain</td>
<td>Subareolar pain</td>
</tr>
<tr>
<td></td>
<td>Tenderness</td>
<td>May have subareolar mass</td>
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<tr>
<td></td>
<td>Erythema</td>
<td>Discharge (variable color)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Heat or ice packs</td>
<td>Broad-spectrum antibiotics and I&amp;O</td>
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<tr>
<td></td>
<td>Continued nursing/pumping</td>
<td>Total duct excision (definitive)</td>
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<tr>
<td></td>
<td>Antibiotics (dicloxacillin/cephalexin)</td>
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<tr>
<td></td>
<td>(Erythromycin if pen-allergic)</td>
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</tr>
<tr>
<td><strong>Abscess</strong></td>
<td>Fluctuant mass</td>
<td>If mass does not resolve, FNA to exclude cancer and U/S to assess presence of abscess</td>
</tr>
<tr>
<td></td>
<td>Purulent nipple discharge</td>
<td>Treatment includes antibiotics, aspiration, or I&amp;O (tends to recur)</td>
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<tr>
<td></td>
<td>Fever, leukocytosis</td>
<td>May develop mammary duct fistula</td>
</tr>
<tr>
<td></td>
<td>Discontinue nursing, IV antibiotics (nafcillin/oxacillin), I&amp;O usually required</td>
<td>A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually <em>S. aureus</em>)</td>
</tr>
</tbody>
</table>
Postpartum Mood Alterations

POSTPARTUM BLUES
- 85% of new mothers, onset day 3-10; extension of the “normal” hormonal changes and
  adjustment to a new baby
- self-limited, should resolve by 2 wk
- manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness,
  fatigue, irritability, poor concentration/responsibility

POSTPARTUM DEPRESSION
- definition: major depression occurring in a woman within 6 mo of childbirth
- epidemiology: 10-20%, risk of recurrence 50%
- risk factors
  ▪ personal or family history of depression (including PPD)
  ▪ prenatal depression or anxiety
  ▪ stressful life situation
  ▪ poor support system
  ▪ unwanted pregnancy
  ▪ colicky or sick infant
- clinical features: suspect if the “blues” last beyond 2 wk, or if the symptoms in the first two
  weeks are severe (e.g. extreme disinterest in the baby, suicidal or homicidal/infanticidal
  ideation)
- assessment: Edinburgh Postnatal Depression Scale or other
- treatment: antidepressants, psychotherapy, supportive care, ECT if refractory
- prognosis: interferes with bonding and attachment between mother and baby so it can have
  long-term effects

POSTPARTUM PSYCHOSIS
- definition: onset of psychotic symptoms over 24-72 h within first month postpartum, can
  present in the context of depression
- epidemiology: rare (0.2%)

Postpartum Care

Postpartum Office Visit at 6 Weeks

Care of Mother (The 10 Bs)
- Be careful: do not use douches or tampons for 4-6 wk post-delivery
- Be fit: encourage gradual increases in walking, Kegel exercises
- Birth control: assess for use of contraceptives; breastfeeding is NOT an effective method of
  birth control (see Gynecology, GY16, for more detail about different contraceptive options
  postpartum)
- Bladder: assess for urinary incontinence, maintain high fluid intake
- Bleeding: (see Lacerations, OB45), 300 µg of RhIG should be given if Rh+ fetus and
  Rh– mother or extensive bleeding at delivery
- Blood pressure: especially if gestational HTN
- Blood tests: glucose, CBC (for anemia as sign of hematomas, retained placenta)
- Blues: (see Postpartum Mood Alterations)
- Bowel: fluids and high-fiber foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain
  meds, doughnut cushion, Sitz baths, ice compresses
- Breast and pelvic exam: watch for Staphylococcal or Streptococcal mastitis/abscess,
  ± Pap smear at 6 wk

Physiological Changes Postpartum
- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains
  firmness
  ▪ should involute ~1 cm below umbilicus per day in first 4-5 d, reaches non-pregnant state in
    4-6 wk postpartum
- ovulation resumes in ~45 d for non-lactating women and within 3-6 mo for lactating women
- lochia: normal vaginal discharge postpartum
  ▪ decreases and changes in color from red (lochia rubra; presence of erythrocytes) → yellow
    (lochia serosa) → white (lochia alba; residual leukorrhea) over 3-6 wk
  ▪ foul-smelling lochia suggests endometritis

The acronym “BUBBLES” for what to ask about when rounding on
postpartum care. Modify this for C/S or vaginal delivery.

Baby care and breastfeeding (latch, amount)
Uterus – firm or boggy?
Bladder function – Voiding well? Dysuria?
Bowel function – Passing gas or stool? Constipated?
Lochia or discharge – Any blood?
Episiotomy/laceration/incision – Pain controlled?
Symptoms of VTE – Dyspnea? Calf pain?
Breastfeeding Problems

- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisture cream, topical steroid if needed
- mastitis: treat promptly (see Postpartum Pyrexia, OB49)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see Breastfeeding and Drugs)

Bladder Dysfunction

- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management: pelvic floor retraining with Kegel exercises, vaginal cones, or pessaries, lifestyle modifications (e.g. limit fluid, caffeine intake)
- surgical management: minimally invasive procedures (tension-free vaginal tape, transobturator tape, midurethral sling)

Puerperal Pain

- "after pains" common in first 3 d due to uterine contractions; encourage simple analgesia
- ice packs can be used on perineum if painful
- encourage regular analgesia and stool softener

Breastfeeding and Drugs

Table 26. Drug Safety During Breastfeeding

<table>
<thead>
<tr>
<th>Safe During Breastfeeding</th>
<th>Contraindicated When Breastfeeding</th>
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<tbody>
<tr>
<td>Analgesics (e.g. acetaminophen, NSAIDs)</td>
<td>Chloramphenicol (bone marrow suppression)</td>
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<tr>
<td>Anticoagulants (e.g. heparin)</td>
<td>Sulphonamides (in G6PD deficiency, can lead to hemolysis)</td>
</tr>
<tr>
<td>Antidepressants (e.g. sertraline, fluoxetine, TCAs)</td>
<td>Nitrofurantoin (in G6PD deficiency, can lead to hemolysis)</td>
</tr>
<tr>
<td>Antiepileptics (e.g. phenytoin, carbamazepine, valproic acid)</td>
<td>Tetracycline</td>
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<tr>
<td>Antihistamines</td>
<td>Lithium</td>
</tr>
<tr>
<td>Antimicrobials (e.g. penicillins, aminoglycosides, cephalosporins)</td>
<td>Anti-neoplastics and immunosuppressants</td>
</tr>
<tr>
<td>β-adrenergics (e.g. propanolol, labetalol)</td>
<td>Psychotropic drugs (relative contraindication)</td>
</tr>
<tr>
<td>Insulin</td>
<td>Steroids</td>
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<tr>
<td>OCP (low dose) – although may decrease breast milk production</td>
<td></td>
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</tbody>
</table>
## Table 27. Common Medications

<table>
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<tr>
<th>Drug Name (Brand Name)</th>
<th>Dosing Schedule</th>
<th>Indications/Comments</th>
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</thead>
<tbody>
<tr>
<td>betamethasone valerate  (Celestone®)</td>
<td>12 mg IM q4h x 2 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>carboprost (Hemabate®)</td>
<td>0.25 mg IM/MM q15min; max 2 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>cefazolin</td>
<td>2 g IV then 1 g q8h</td>
<td>GBS prophylaxis (penicillin allergic and not at risk for anaphylaxis)</td>
</tr>
<tr>
<td>clindamycin</td>
<td>900 mg IV q8h</td>
<td>GBS prophylaxis (penicillin allergic and at risk for anaphylaxis); Also used in endometritis</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>6 mg IM q12h x 4 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>dinoprostone (Cervidil®: PGE2 impregnated thread)</td>
<td>10 mg PV (remove after 12 h) max 3 doses</td>
<td>Induction of labor; Advantage: can remove if uterine hyperstimulation</td>
</tr>
<tr>
<td>doxylamine succinate (Diclegis®)</td>
<td>2 tabs qhs + 1 tab qAM + 1 tab qPM max 8 tabs/d</td>
<td>Each tablet contains 10 mg doxylamine succinate with vitamin B6; Used for hyperemesis gravidarum</td>
</tr>
<tr>
<td>erythromycin</td>
<td>500 mg IV q6h</td>
<td>GBS prophylaxis (penicillin allergic and at risk for anaphylaxis)</td>
</tr>
<tr>
<td>folic acid</td>
<td>0.4-1 mg PO OD x 1-3 mo preconception and T1; 5 mg PO OD with past Hx of NTD</td>
<td>Prevention of oNTD</td>
</tr>
<tr>
<td>methotrexate</td>
<td>50 mg/m² IM or 50 mg PO x 1 dose</td>
<td>For ectopic pregnancy or medical abortion</td>
</tr>
<tr>
<td>ergotamine</td>
<td>0.25 mg IM or IV bolus 0.125 mg q6min up to 1.25 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>misoprostol (Cytotec®)</td>
<td>800-1000 µg PR x 1 dose 400 µg PO x 1 dose or 800 µg PV x 1 dose, 3-7 d after methotrexate</td>
<td>For treatment of PPH; For medical abortion/retained products of conception; Also used for NSAID-induced ulcers (warn patients of contraindications)</td>
</tr>
<tr>
<td>oxytocin (Pitocin®)</td>
<td>0.5-2.0 mL/min IV, or 10 U/L NS increase by 1-2 mL/min q20-60min max 36-48 mL/min 10 U IM at delivery of anterior shoulder and of placenta 20 U/L NS or RL IV continuous infusion</td>
<td>Augmentation of labor (also induction of labor); Prevention of uterine atony; Treatment of uterine atony</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>5 million U IV then 2.5 million U IV q4h until delivery</td>
<td>GBS prophylaxis</td>
</tr>
<tr>
<td>PGE2 gel (Prostin® gel)</td>
<td>0.5 mg PV q6-12h x max 3 doses</td>
<td>Induction of labor</td>
</tr>
<tr>
<td>Rh IgG (Rhogam®)</td>
<td>300 µg IM x 1 dose</td>
<td>Given to Rh negative women: • Routinely at 28 wk GA; • Within 72 h of birth of Rh +ve fetus; • Positive Kleihauer-Betke test; • With any invasive procedure in pregnancy; • Ectopic pregnancy; • Antepartum hemorrhage; • Miscarriage or therapeutic abortion (dose: 50 µg IM only)</td>
</tr>
</tbody>
</table>

**Common Discharge Medications**

- Oxycodone IR 5-10 mg PO q4-6h PRN
- Docusate sodium 100 mg PO bid

---

**Misoprostol (Cytotec®)** is also indicated to protect against NSAID-induced gastric ulcers in non-pregnant individuals. The use of misoprostol for cytoprotection is contraindicated in pregnancy; warn female patients of this contraindication.
# Ophthalmology

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<td>Lacrimal Apparatus</td>
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<td>Dry Eye Syndrome</td>
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<td>Dacryocystitis</td>
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<td>Epiphora (Tearing)</td>
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<td>Dacryoadenitis</td>
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<td>Lids and Lashes</td>
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<td>Lid Swelling</td>
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<td>Hordeolum (Stye)</td>
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<td>Vitreous Hemorrhage</td>
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<td>Endophthalmitis and Vitritis</td>
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<td>Retina</td>
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<td>Branch Retinal Artery Occlusion</td>
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<td>Retinitis Pigmentosa</td>
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<td>Leber's Congenital Amaurosis</td>
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<td>Age-Related Macular Degeneration</td>
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<td>Glaucoma</td>
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<td>Primary Open-Angle Glaucoma</td>
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<td>Blow-Out Fracture</td>
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### Acronyms

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<th>Definition</th>
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<tr>
<td>AION</td>
<td>anterior ischemic optic neuropathy</td>
</tr>
<tr>
<td>AMD</td>
<td>age-related macular degeneration</td>
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<tr>
<td>BCVA</td>
<td>best corrected visual acuity</td>
</tr>
<tr>
<td>BRAO</td>
<td>branch retinal artery occlusion</td>
</tr>
<tr>
<td>BRVO</td>
<td>branch retinal vein occlusion</td>
</tr>
<tr>
<td>C/D</td>
<td>cup to disc ratio</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CRAO</td>
<td>central retinal artery occlusion</td>
</tr>
<tr>
<td>D</td>
<td>diopter</td>
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<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>DR</td>
<td>diabetic retinopathy</td>
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<tr>
<td>EDM</td>
<td>extraocular movement</td>
</tr>
<tr>
<td>FML</td>
<td>fluromethalone</td>
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<tr>
<td>GAT</td>
<td>Goldmann applanation tonometry</td>
</tr>
<tr>
<td>GCA</td>
<td>giant cell arteritis</td>
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<tr>
<td>HRT</td>
<td>Heidelberg retinal tomography</td>
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<tr>
<td>INO</td>
<td>intranuclear ophtalmoplegia</td>
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<tr>
<td>IOP</td>
<td>intraocular pressure</td>
</tr>
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<td>IOI</td>
<td>laser-assisted in situ keratomileusis</td>
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<tr>
<td>M/F</td>
<td>multiple sclerosis</td>
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<td>OCT</td>
<td>optical coherence tomography</td>
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<tr>
<td>OHT</td>
<td>ocular hypertension</td>
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<tr>
<td>PACG</td>
<td>primary angle-closure glaucoma</td>
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<td>PDR</td>
<td>proliferative diabetic retinopathy</td>
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<tr>
<td>PDT</td>
<td>photodynamic therapy</td>
</tr>
<tr>
<td>PERLA</td>
<td>pupils equal and reactive to light and accommodation</td>
</tr>
<tr>
<td>PGAG</td>
<td>primary open-angle glaucoma</td>
</tr>
<tr>
<td>PK</td>
<td>photokeratectomy</td>
</tr>
<tr>
<td>PVD</td>
<td>posterior vitreous detachment</td>
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<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RAPD</td>
<td>retinal detachment</td>
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<tr>
<td>ROP</td>
<td>retinopathy of prematurity</td>
</tr>
<tr>
<td>RPE</td>
<td>retinal pigment epithelium</td>
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<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
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<tr>
<td>SPK</td>
<td>superficial punctate keratitis</td>
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<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>YAG</td>
<td>yttrium aluminum garnet</td>
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</tbody>
</table>

### Basic Anatomy Review

**Figure 1. Anatomy of the eye**

**Figure 2. Layers of the retina**
Figure 3. Tear drainage from the eye (lacrimal apparatus)

Differential Diagnoses of Common Presentations

Loss of Vision

- Transient (seconds to hours)
  - Cornea/Anterior Segment: Corneal edema, Hyphema, Acute angle-closure glaucoma, Trauma/foreign body
  - Vitreous/Retina/Optic Nerve: Vitreous hemorrhage, Retinal artery/vein occlusion, Acute macular lesion, Optic neuritis, Temporal arteritis, Anterior ischemic optic neuropathy (AION)
  - Cortical/Other: Occipital infarction/hemorrhage, Cortical blindness, Functional (non-organic, diagnosis of exclusion)

- Acute (seconds to days)
  - Cornea/Anterior Segment: Corneal dystrophy/scarring/edema, Trauma/foreign body
  - Vitreous/Retina/Optic Nerve: AMD, DR, Retinal vascular insufficiency, Compressive optic neuropathy (intracranial mass, orbital mass), Intraocular neoplasm, Retinitis pigmentosa
  - Cortical/Other: Pituitary adenoma, Medication-induced (sildenafil, amiodarone), Nutritional deficiency, Papilledema

- Chronic (weeks to months)
  - Cornea/Anterior Segment: Trauma/foreign body
  - Vitreous/Retina/Optic Nerve: Retinal artery/vein occlusion, RD

Top 3 Differential Diagnosis of Acute Loss of Vision
- Trauma/foreign body
- Retinal artery/vein occlusion
- RD

Top 3 Differential Diagnosis of Chronic Loss of Vision
Reversible
- Cataract
- Refractive error
- Corneal dystrophy

Irreversible
- AMD
- Glaucoma
- DR

Note: Anti-VEGF treatment for exudative AMD and diabetic macular edema may reverse some vision loss

Figure 4. Loss of vision
Red Eye

- lids/orbit/lacrimal system
  - hordeolum/chalazion
  - blepharitis
  - entropion/ectropion
  - foreign body/laceration
dacrystocystitis/dacryoadenitis
- conjunctiva/sclera
  - subconjunctival hemorrhage
  - conjunctivitis
  - dry eyes
  - pterygium
  - episcleritis/scleritis
  - preseptal/orbital cellulitis
- cornea
  - foreign body (including contact lens)
  - keratitis
  - abrasion, laceration
  - ulcer
- anterior chamber
  - anterior uveitis (iritis, iridocyclitis)
  - acute angle-closure glaucoma
  - hyphema (blood in anterior chamber)
  - hypopyon (pus in anterior chamber)
- other
  - trauma
  - post-operative
  - endophthalmitis

Ocular Pain

- differentiate from eye fatigue (asthenopia)
- herpes zoster prodrome
- trauma/foreign body
- keratitis
- corneal abrasion, corneal ulcer
- acute angle-closure glaucoma
- acute uveitis
- scleritis, episcleritis
- optic neuritis

Photophobia (Severe Light Sensitivity)

- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis, encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

Diplopia (Double Vision)

- binocular diplopia (occurs with both eyes open, eliminated with occlusion of either eye)
  - strabismus, CN palsy (III, IV, VI) secondary to ischemia, DM, tumor, trauma, myasthenia gravis, muscle restriction/entrapment, thyroid ophthalmopathy, INO secondary to multiple sclerosis, brainstem infarct
- monocular diplopia (occurs with one eye open, remains with occlusion of unaffected eye)
  - refractive error, strands of mucus in tear film, keratoconus, cataracts, dislocated lens, peripheral iridotomy

Ocular Problems in the Elderly

- blepharitis
- ptosis
- entropion, ectropion
- dry eyes, epiphora (excessive tearing)
- presbyopia
- cataracts
- glaucoma
- AMD
- retinal artery/vein occlusion
- temporal arteritis (arteritic ischemic optic neuropathy)

Ocular Problems in the Contact Lens Wearer

- SPK from dry eyes
- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis/contact lens allergy
- sterile corneal infiltrates (immunologic)
- infected ulcers (*Pseudomonas, Acanthamoeba*)

Flashes of Light (Photopsia)

- PVD
- retinal tear/detachment
- migraine with aura

Acute Painless Vision Loss

- vitreous hemorrhage
- retinal artery/vein occlusion
- RD
- AION
- optic neuritis
- amaurosis fugax
Table 1. Common Differential Diagnoses of Red Eye

<table>
<thead>
<tr>
<th></th>
<th>Conjunctivitis</th>
<th>Acute Iritis</th>
<th>Acute Angle-Closure Glaucoma</th>
<th>Keratitis (Corneal Abrasion/Ulcer)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>Bacteria: purulent</td>
<td>No</td>
<td>No</td>
<td>Profuse tearing</td>
</tr>
<tr>
<td></td>
<td>Virus: serous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allergy: mucous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>No</td>
<td>++ (tender globe)</td>
<td>+++ (nausea)</td>
<td>+++ (on blinking)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>No</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>No</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Pupil</td>
<td>Normal</td>
<td>Smaller</td>
<td>Fixed in mid-dilation</td>
<td>Same or smaller</td>
</tr>
<tr>
<td>Injection</td>
<td>Conjunctiva with limbal pallor</td>
<td>Ciliary flush</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td>Cornea</td>
<td>Normal</td>
<td>Keratic precipitates</td>
<td>Cloudy</td>
<td>Infiltrate, edema, epithelial defects</td>
</tr>
<tr>
<td>IOP</td>
<td>Normal</td>
<td>Varies</td>
<td>Increased markedly</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>Anterior Chamber</td>
<td>Normal</td>
<td>++ + Cells and flare</td>
<td>Shallow</td>
<td>Cells and flare or normal</td>
</tr>
<tr>
<td>Other</td>
<td>Large, tender pre-auricular node(s) if viral</td>
<td>Posterior synechiae</td>
<td>Colored halos</td>
<td>Nausea and vomiting</td>
</tr>
</tbody>
</table>

Ocular Emergencies

These require urgent consultation to an ophthalmologist for management

Sight Threatening
- lid/globe lacerations
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute angle-closure glaucoma
- CRAO
- intraocular foreign body
- RD (especially when macula threatened)
- endophthalmitis

Life Threatening
- proptosis (rule out cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or neoplastic lesion)
- papilledema (must rule out intracranial mass lesion)
- orbital cellulitis
- GCA
- leukocoria: white reflex (absent red reflex, must rule out retinoblastoma)

The Ocular Examination

Visual Acuity – Distance
- Snellen Acuity (Figure 5) = testing distance (usually 20 feet or 6 meters) / smallest line patient can read on the chart
  - e.g. 20/40 = what the patient can see at 20 feet (numerator), what a “normal” person can see at 40 feet (denominator)
- distance visual acuity should be tested with distance glasses on in order to obtain best corrected visual acuity
- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
- legal blindness is BCVA that is ≤20/200 in best eye

Figure 5. Ophthalmology nomenclature for VA

OD = oculus dexter = right eye
OS = oculus sinister = left eye
OU = oculus uterque = both eyes

Example 1
V
20/40 –1
20/80 + 2 → 20/25 PH

Example 2
 CC
CF 3’
HM

Note: RIGHT EYE visual acuity always listed on top.
V = Vision
SC = Without correction
CC = With correction
20/40 -1 = All except one letter of 20/40
20/80 + 2 = All of 20/80 plus two letters of 20/70
PH = Visual acuity with pinhole correction
CF = Counting fingers
HM = Hand motion

Normal Infant and Child Visual Acuity
- 6-12 mo: 20/120
- 1-2 yr: 20/60
- 2-4 yr: 20/20
Visual Acuity – Near
- use pocket vision chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance VA possible (e.g. immobile patient, no distance chart available)

Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics
- newborns
  - VA cannot be tested
- 3 mo - 3 yr (can only assess visual function, not acuity)
  - test each eye for fixation symmetry using an interesting object
  - normal function noted as “CSM” = central, steady, and maintained
- 3 yr until alphabet known
  - pictures or letter cards/charts such as HOTV or Sheridan-Gardner test (children point to optotypes on a provided matching card)
  - tumbling “E” chart

Color Vision
- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye, specify incorrect plates
- important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
- note: red-green color blindness is sex-linked and occurs in 7-10% of males

VISUAL FIELDS
- test "visual fields by confrontation" (4 quadrants, each eye tested separately) for estimation of visual field loss
- accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- use Amsler grid (tested separately) to test for central or paracentral scotomas (island-like gaps in the vision) in patients with AMD

PUPILS
- use reduced room illumination with patient focusing on distant object to prevent “near reflex”
- examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
- RAPD with swinging flashlight test
- test pupillary constriction portion of near reflex by bringing object close to patient’s nose
- “normal” pupil testing often noted as PERLA (pupils equal, round, and reactive to light and accommodation)

ANTERIOR CHAMBER DEPTH
- shine light tangentially from temporal side
- if >2/3 of nasal side of iris in shadow → shallow anterior chamber

The van Herick Method
- shine thin-angled slit beam onto the peripheral cornea of each eye
- estimate depth between the posterior surface of the cornea and the iris as a proportion of corneal thickness
- follow-up with gonioscopy for ratios ≤1/4

Gonioscopy
- allows direct visualization of the angle structures
- angle considered open if trabecular meshwork, scleral spur, and iris processes are visualized
- angle considered narrow (occludable) if only Schwalbe’s line or a small portion of the trabecular meshwork is seen

EXTRAOCULAR MUSCLES

Alignment
- Hirschberg corneal reflex test
  - examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  - shine light into patient’s eyes from ~30 cm away
  - corneal light reflex should be symmetric and at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing) (see Strabismus, OP38)
Movement
- examine movement of eyeball through six cardinal positions of gaze
- ask patient if diplopia is present in any position of gaze
- observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end-gaze is usually normal
- see sidebar for cranial nerve innervation of extraocular muscles

Diplopia
- major symptom associated with dysfunction of extraocular muscles or abnormalities of the motor nerves innervating these muscles
- must determine whether diplopia is monocular or binocular
- determine whether diplopia was sudden onset (due to an acute event such as ischemia) or gradual (due to progressive process such as tumor or inflammation)
- with myasthenia gravis, diplopia and ptosis usually worsen on prolonged upgaze; can rule out with a Tensilon® test (see Neurology, N38)
- if suspect compressive lesion (most commonly seen with CN III palsy with a blown pupil), need MRI and angiography to rule out aneurysm or tumor
- new-onset diplopia that disappears with occlusion of either eye (binocular diplopia) needs urgent referral while chronic binocular diplopia and monocular diplopia should be referred non-urgently

**Figure 9. Diplopia**

**EXTERNAL EXAMINATION**
- four Ls
  - lymph nodes (preauricular, submandibular)
  - lids
  - lashes
  - lacrimal system

**SLIT-LAMP EXAMINATION**
- systematically examine all structures of the anterior segment and anterior vitreous (for structures see Figure 1)
- when necessary, use
  - fluorescein dye: stains Bowman’s membrane in de-epithelialized cornea; dye appears green with cobalt blue filtered light
  - Rose Bengal dye: stains devitalized corneal epithelium
- special lenses (78 or 90 D) used with the slit-lamp allow a binocular, stereoscopic view of the fundus and vitreous

**Figure 10. Slit-lamp examination note**

**Figure 8. Diagnostic positions of gaze for isolated primary actions of extraocular muscles**

**Extraocular Muscle Innervations**
- LR6 SO4 AE3
- Lateral Rectus via CN VI
- Superior Oblique via CN IV
- All Else via CN III (superior, medial, and inferior rectus, inferior oblique)

**Aqueous Flare**
- Resembles dust particles in a beam of light
- Results from protein leaking from blood vessels
- Distinguish from aqueous cells (individual cells in anterior chamber)
TONOMETRY
- measurement of IOP
- normal range is 10-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by
  - Goldmann Applanation Tonometry (GAT): gold standard, performed using the slit-lamp with special tip (prism)
  - Tono-Pen®: benefit is portability and use of disposable probe tips. Use when cornea is scarred/asymmetric (GAT inaccurate)
  - air puff (non-contact and least reliable)
- use topical anesthetic for GAT and Tono-Pen

OPHTHALMOSCOPY/FUNDOSCOPY
- performed with
  - direct ophthalmoscope (monocular with small field of view, only posterior pole visualized)
  - slit-lamp with 78 or 90 D lens (binocular view, visualization to mid-periphery of retina)
  - indirect ophthalmoscopy with headlamp and 20 or 28 D lens (binocular view, visualization of entire retina to ora serrata/edge of retina)
- best performed with pupils dilated (for list of mydriatics and cycloplegics see Table 11, OP45)
  1. assess red reflex
     - light reflected off the retina produces a “red reflex” when viewed from ~1 foot away
     - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract)
  2. examine the posterior segment of the eye (Figure 10)
     - vitreous
     - optic disc (color, C:D ratio, sharpness of disc margin)
     - macula (~2 disc diameters temporal to disc), fovea (foveal light reflex)
     - retinal vessels
     - retinal background
- contraindications to pupillary dilatation
  - shallow anterior chamber – can precipitate acute angle-closure glaucoma
  - iris-supported anterior chamber lens implant
  - potential neurologic abnormality requiring pupil evaluation
  - use caution with cardiovascular disease – mydriatics may cause tachycardia

Optics

REFRACTION
- two techniques used
  - flash/streak retinoscopy: refractive error determined objectively by the examiner using lenses and retinoscope
  - manifest: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
- a typical lens prescription would contain
  - sphere power in D (measurement of refractive power of lens, equal to reciprocal of focal length in meters)
  - cylinder power in D to correct astigmatism (always positive value)
  - axis of cylinder in degrees
  - “add” (bifocal/progressive reading lens) for presbyopes
    - e.g. -1.50 + 1.00 x 120 degrees, add +2.00

REFRACTIVE EYE SURGERY
- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK and LASIK (see Surgical Ophthalmology, OP44)
- potential risks/side-effects: infection, under/overcorrection, decreased night vision (nyctalopia), corneal haze, dry eyes, regression, complete sever of corneal flap (LASIK only)
Table 2. Optics

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emmetropia</td>
<td>Image of distant objects focus exactly on the retina (Figure 12)</td>
<td>No refractive error</td>
<td></td>
</tr>
<tr>
<td>Myopia</td>
<td>Globe too long relative for refractive mechanisms, or refractive mechanisms too strong</td>
<td>“Nearsightedness”</td>
<td>Correct with negative diopeter/ concave/ “negative” lenses to diverge light rays</td>
</tr>
<tr>
<td></td>
<td>Light rays from distant object focus in front of retina → blurring of (distance) vision (Figure 12)</td>
<td>Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with DM or cataracts</td>
<td>Refractive eye surgery</td>
</tr>
<tr>
<td></td>
<td>Blurring of distance vision; near vision usually unaffected</td>
<td>Prevalence: 30-40% in U.S. population</td>
<td>Retinal tear/ detachment, macular hole, open angle glaucoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other complications that are not prevented with refractive correction</td>
</tr>
<tr>
<td>Hyperopia</td>
<td>Globe too short relative to refractive mechanisms, or refractive mechanisms too weak</td>
<td>“Farsightedness”</td>
<td>When symptomatic, correct with positive diopeter/ convex/ “plus” lenses to converge light rays</td>
</tr>
<tr>
<td></td>
<td>Light rays from distant object focus behind retina → blurring of near = distant vision (Figure 12)</td>
<td>Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia (see Strabismus, OP38)</td>
<td>Refractive eye surgery</td>
</tr>
<tr>
<td></td>
<td>May be developmental or due to any etiology that shortens globe</td>
<td>30s-40s: blurring of distance vision due to decreased accommodation</td>
<td>Angle-closure glaucoma, particularly later in life as lens enlarges</td>
</tr>
<tr>
<td>Astigmatism</td>
<td>Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped)</td>
<td>Affects approximately 30% of population, with prevalence increasing with age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Two types:</td>
<td>Mild astigmatism unnoticeable</td>
<td>Correct with cylindrical lens (if regular), try contact lens (if irregular)</td>
</tr>
<tr>
<td></td>
<td>Regular – curvature uniformly different in meridians at right angles to each other</td>
<td>Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches</td>
<td>Refractive eye surgery</td>
</tr>
<tr>
<td></td>
<td>Irregular – distorted cornea caused by injury, keratoconus (cone-shaped cornea), corneal scar, or severe dry eye</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presbyopia</td>
<td>Normal aging process (&gt;40 yr)</td>
<td>If initially emmetropic, person begins to hold reading material farther away, but distance vision remains unaffected</td>
<td>Correct with positive diopeter/ convex/ “plus” lenses for reading</td>
</tr>
<tr>
<td></td>
<td>Hardening/reduced deformability of lens results in decreased accommodative ability</td>
<td>If initially myopic, person removes distance glasses to read</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accommodative power is 14D at age 10, diminishes to 3.5D by age 40</td>
<td>If initially hyperopic, symptoms of presbyopia occur earlier</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anisometropia</td>
<td>Difference in refractive errors between eyes</td>
<td></td>
<td>Second most common cause of amblyopia in children</td>
</tr>
</tbody>
</table>

Imaging Modalities

- adaptive optics scanning laser ophthalmology – optical coherence tomography (SLO-OCT)
  - combines the surface detail of confocal ophthalmoscopy with the internal detail of OCT
  - allows 3D OCT images, volume and area maps, and retinal thickness maps, at the resolution of living rods and cones
  - can visualize photoreceptors, nerve fibers and blood cells in retinal capillaries
- CT, MRI
  - orbital imaging, particularly in orbital trauma and neuro-ophthalmology
- fluorescein angiography
  - non-invasive evaluation of vascular pattern of the fundus
  - commonly used in AMD, DR, retinal vascular diseases
- indocyanine green angiography
  - uses infra-red light and intravenous ICG dye for imaging of choroidal structure
  - particularly useful to detect polypoidal vasculopathy (variant of AMD) more commonly present among Asian patients
• HRT
  - confocal scanning laser tomography of retinal nerve head and surrounding nerve fiber layer
  - used to assess extent of structural glaucomatous changes

• OCT
  - non-invasive, cross-sectional, high-resolution imaging of vitreous, retinal layers, optic nerve
  - commonly used to assess macular pathology/edema/holes/cysts, AMD progression, epiretinal membrane, RD

• anterior segment optical coherence tomography (AS-OCT)
  - non-invasive, cross-sectional, high-resolution imaging of cornea, aqueous, iris and lens

• perimetry
  - quantitative evaluation of visual fields, used to screen for scotomas and monitor progression (e.g. in glaucoma)

• ultrasonography
  - evaluation of orbit in real-time. A-scans (one-dimensional), B-scans (two-dimensional), and Doppler are all used (e.g. large RDs, foreign bodies, monitoring intraocular tumors)

## The Orbit

### Globe Displacement

<table>
<thead>
<tr>
<th>Exophthalmos (Proptosis)</th>
<th>Enophthalmos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>Anterior displacement (protrusion) of the globe</td>
<td>Posterior displacement (retraction) of the globe</td>
</tr>
<tr>
<td>Exophthalmos generally refers to an endocrine etiology or protrusion of &gt;18 mm (as measured by a Hertel exophthalmometer)</td>
<td></td>
</tr>
<tr>
<td>Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of &lt;18 mm</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>CT/MRI head/orbits, ultrasound orbits, thyroid function tests</td>
<td>Note: rule out pseudoexophthalmos (e.g. lid retraction)</td>
</tr>
<tr>
<td></td>
<td>Graves' disease (unilateral or bilateral, most common cause in adults)</td>
</tr>
<tr>
<td></td>
<td>Orbital cellulitis (unilateral, most common cause in children)</td>
</tr>
<tr>
<td></td>
<td>1° or 2° orbital tumors</td>
</tr>
<tr>
<td></td>
<td>Orbital/retrorublar hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Cavernous sinus thrombosis or fistula</td>
</tr>
<tr>
<td></td>
<td>CT/MRI orbits</td>
</tr>
<tr>
<td></td>
<td>&quot;Blow-out&quot; fracture (see Ocular Trauma, OP42)</td>
</tr>
<tr>
<td></td>
<td>Orbital fat atrophy</td>
</tr>
<tr>
<td></td>
<td>Congenital abnormality</td>
</tr>
<tr>
<td></td>
<td>Metastatic disease</td>
</tr>
</tbody>
</table>

#### Preseptal Cellulitis

- infection of soft tissue anterior to orbital septum

**Etiology**

- usually follows periorbital trauma or dermal infection

**Clinical Features**

**Treatment**

- systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
  - e.g. amoxicillin-clavulanic acid
- if severe or child <1 yr, treat as orbital cellulitis

#### Orbital Cellulitis

- **OCULAR and MEDICAL EMERGENCY**
- inflammation of orbital contents posterior to orbital septum
- common in children, elderly, and immunocompromised

**Etiology**

- usually secondary to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

**Clinical Features**

**Treatment**

- admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
- surgical drainage of abscess with close follow-up, especially in children
Complications

• optic nerve inflammation, cavernous sinus thrombosis, meningitis, and brain abscess with possible loss of vision, death

Table 4. Clinical Features of Preseptal and Orbital Cellulitis

<table>
<thead>
<tr>
<th>Finding</th>
<th>Preseptal Cellulitis</th>
<th>Orbital Cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>May be present</td>
<td>Present</td>
</tr>
<tr>
<td>Lid edema</td>
<td>Moderate to severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Conjunctival injection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Chemosis</td>
<td>Absent or mild</td>
<td>Marked</td>
</tr>
<tr>
<td>Proptosis</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Pain on eye movement</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Ocular mobility</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Vision</td>
<td>Normal</td>
<td>Diminished ± diplopia</td>
</tr>
<tr>
<td>RAPD</td>
<td>Absent</td>
<td>May be seen</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>ESR</td>
<td>Normal or elevated</td>
<td>Elevated</td>
</tr>
<tr>
<td>Additional findings</td>
<td>Skin infection</td>
<td>Sinusitis, dental abscess</td>
</tr>
</tbody>
</table>

Lacrimal Apparatus

• tear film made up of three layers
  ▪ outer oily layer (reduces evaporation): secreted by the Meibomian glands
  ▪ middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  ▪ inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells
• tears drain from the eyes through the upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrimal duct → nasal cavity behind inferior concha (Figure 3)

Dry Eye Syndrome (Keratoconjunctivitis Sicca)

Etiology

• aqueous-deficient (lacrimal pathology)
  ▪ Sjögren syndrome (autoimmune etiology e.g. RA, SLE)
  ▪ non-Sjögren syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy, anticholinergics, antihistamines, diuretics, β-blockers)
• evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  ▪ Meibomian gland dysfunction (posterior blepharitis)
  ▪ vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  ▪ eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  ▪ preserved topical ocular medications
  ▪ contact lenses, allergic conjunctivitis
• overlap of mixed etiologies common

Clinical Features

• dry eyes, red eyes, foreign body sensation, blurred vision, tearing
• slit-lamp exam: decreased tear meniscus, decreased tear break-up time (normally should be 10 s), SPK

Investigations

• surface damage observed with fluorescein/Rose Bengal staining
• decreased distance in Schirmer’s test

Complications

• erosions and scarring of cornea

Treatment

• medical: preservative-free artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used more than q1h PRN)
  ▪ for severe cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) can be used
• procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
• treat underlying cause

Role of Oral Corticosteroids in Orbital Cellulitis


Purpose: To evaluate the role of oral corticosteroids as an anti-inflammatory adjunct for the treatment of orbital cellulitis.

Study: RCT. Patients with acute onset (within 14 d) of orbital cellulitis with or without abscess. 21 patients total (7 patients in group 1: standard intravenous antibiotics; 14 patients in group 2: adjuvant steroids).

Results: Patients in group 2 showed earlier resolution of periorbital edema, conjunctival chemosis, pain, proptosis, and EOM deficits, including decreased duration of intravenous antibiotics and hospital stay (p<0.05 for all).

Conclusion: The use of oral steroids as an adjunct to intravenous antibiotics for orbital cellulitis may decrease inflammatory symptoms with a low risk of worsening infection.

Long-term use of artificial tears with preservatives should be avoided when treating dry eyes
Epiphora (Excessive Tearing)

Etiology
- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex (crocodile tears)

Investigations
- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

Treatment
- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy (see Surgical Ophthalmology, OP44) – forming a new connection between the lacrimal sac and the nasal cavity

Dacryocystitis
- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- commonly associated with S. aureus, S. pneumoniae, Pseudomonas species

Clinical Features
- pain, swelling, redness over lacrimal sac at medial canthus
- epiphora, crusting, ± fever
- digital pressure on the lacrimal sac may extrude pus through the punctum
- in the chronic form, epiphora may be the only symptom

Treatment
- warm compresses, nasal decongestants, systemic and topical antibiotics
- if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy (see Surgical Ophthalmology, OP44)

Dacryoadenitis
- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: S. aureus, mumps, EBV, herpes zoster, N. gonorrhoeae
- chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

Clinical Features
- pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

Treatment
- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder

Lids and Lashes

Lid Swelling

Etiology
- commonly due to allergy, with shriveling of skin between episodes
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatchalasis (loose skin due to aging or heredity)
- lid cellulitis, thyroid disease (e.g. myxedema), trauma, chemosis
Ptosis

- drooping of upper eyelid

Etiology
- **aponeurotic**: disinsertion or dehiscence of levator aponeurosis (most common)
  - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- **mechanical**
  - incomplete opening of eyelid due to mass or scarring
- **neuromuscular**
  - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  - CN III palsy
  - Horner’s syndrome (see *Constricted Pupil, Horner’s Syndrome, OP32*)
- **congenital**
- **pseudoptosis** (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)

Treatment
- surgery

Trichiasis

- **eyelashes turned inwards**
  - may result from chronic inflammatory lid diseases (e.g. blepharitis), Stevens-Johnson syndrome, trauma, burns
  - patient complains of red eye, foreign body sensation, tearing
  - may result in corneal ulceration and scarring

Treatment
- topical lubrication, eyelash plucking, electrolysis, cryotherapy

Entropion

- lid margin turns in towards globe causing tearing, foreign body sensation, and red eye
  - most commonly affects lower lid
  - may cause abrasions with secondary corneal scarring

Etiology
- **involutional** (aging)
- **cicatricial** (herpes zoster, surgery, trauma, burns)
- **orbicularis oculi muscle spasm**
- **congenital**

Treatment
- lubricants, evert lid with tape, surgery

Ectropion

- lid margin turns outward from globe causing tearing and possibly exposure keratitis

Etiology
- **involutional** (aging)
- **paralytic** (CN VII palsy)
- **cicatricial** (burns, trauma, surgery)
- **mechanical** (lid edema, tumor, herniated fat)
- **congenital**

Treatment
- topical lubrication, surgery

Hordeolum (Stye)

- **acute inflammation of eyelid gland**: either Meibomian glands (internal lid) or glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)
- infectious agent is usually *S. aureus*
- painful, red swelling of lid

Treatment
- warm compresses, lid care, gentle massage
- topical antibiotics (e.g. erythromycin ointment bid)
- usually resolves in 2-5 d
Chalazion
- chronic granulomatous inflammation of Meibomian gland often preceded by an internal hordeolum
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, Meibomian gland carcinoma

Treatment
- warm compresses
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy

Blepharitis
- inflammation of lid margins

Etiology
- two main types
  - staphylococcal (S. aureus): ulcerative: dry scales
  - seborrheic: no ulcers, greasy scales

Clinical Features
- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids ("toothpaste sign")

Complications
- recurrent chalazia
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

Treatment
- warm compresses and lid scrubs with diluted "baby shampoo"
- topical or systemic antibiotics as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids

Xanthelasma
- eyelid xanthoma (lipid deposits in dermis of lids)
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (approximately 50% of patients)
- common in the elderly, more concerning in the young

Treatment
- excision for cosmesis only, commonly recurs

Conjunctiva
- thin, vascular mucous membrane/epithelium
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

Pinguecula
- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea
- associated with sun and wind exposure, aging
- common, benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops
**Pterygium**

- fibrovascular triangular encroachment of epithelial tissue onto the cornea, usually nasally
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (5%)

**Subconjunctival Hemorrhage**

- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, HTN
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- if recurrent, consider medical/hematologic workup

**Conjunctivitis**

**Etiology**

- infectious
  - bacterial, viral, chlamydial, fungal, parasitic
- non-infectious
  - allergic: atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
- secondary to another disorder: dacryocystitis, dacryoadenitis, cellulitis, Kawasaki disease

**Clinical Features**

- red eye (conjunctival injection often with limbal pallor), chemosis, subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, lid edema
- preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)

**ALLERGIC CONJUNCTIVITIS**

**Atopic**

- associated with rhinitis, asthma, dermatitis, hay fever
- small papillae, chemosis, thickened and erythematous lids, corneal neovascularization
- seasonal (pollen, grasses, plant allergens)
- treatment: cool compresses, antihistamine, mast cell stabilizer (e.g. ketotifen, olopatadine)

**Giant Papillary Conjunctivitis**

- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva
- treatment: clean, change or discontinue use of contact lens

**Vernal Conjunctivitis**

- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 yr then resolves
- treatment: consider topical steroid, topical cyclosporine (by ophthalmologist)

**VIRAL CONJUNCTIVITIS**

- serous discharge, lid edema, follicles
- subepithelial corneal infiltrates
- may be associated with rhinorrhea
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye
- mainly due to adenovirus – highly contagious for up to 12 d

**Treatment**

- cool compresses, topical lubrication
- usually self-limiting (7-12 d)
- proper hygiene is very important
**BACTERIAL CONJUNCTIVITIS**
- purulent discharge, lid swelling, papillae, conjunctival injection, chemosis
- common agents include *S. aureus*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*
- in neonates or if sexually active must consider *N. gonorrhoeae* (invades cornea to cause keratitis)
- *C. trachomatis* is the most common cause in neonates

**Treatment**
- topical broad-spectrum antibiotic
- systemic antibiotics if indicated, especially in neonates and children
- usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment

**CHLAMYDIAL CONJUNCTIVITIS**
- caused by *C. trachomatis*
- affects neonates (ophthalmia neonatorum) on day 3-5, sexually active individuals
- causes trachoma and inclusion conjunctivitis

**Trachoma**
- leading infectious cause of blindness in the world
- severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
- initially, follicles on superior palpebral conjunctiva
- treatment: topical and systemic tetracycline

**Inclusion Conjunctivitis**
- chronic conjunctivitis with follicles and subepithelial infiltrates
- most common cause of conjunctivitis in newborns
- prevention: topical erythromycin at birth
- treatment: topical and systemic tetracycline, doxycycline, or erythromycin

---

**Sclera**
- white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
- continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
- episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

**Episcleritis**
- immunologically mediated inflammation of episclera
- 1/3 bilateral; simple (80%) or nodular (20%)
- more frequent in women than men (3:1)

**Etiology**
- mostly idiopathic
- in 1/3 of cases, associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, syphilis), inflammatory bowel disease, rosacea, atopy

**Clinical Features**
- usually asymptomatic; may have discomfort, heat sensation, red eye (often interpalpebral), rarely pain
- sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
- blanches with topical phenylephrine (constricts superficial conjunctival vessels)

**Treatment**
- generally self limited, recurrent in 2/3 of cases
- topical steroid for 3-5 d if painful (prescribed and monitored by ophthalmologist)

**Scleritis**
- usually bilateral: diffuse, nodular, or necrotizing
- anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing
- posterior scleritis: rapidly progressive blindness, may cause exudative RD
- more common in women and elderly
Etiology
- may be a manifestation of systemic disease
- collagen vascular disease, e.g., SLE, RA, ankylosing spondylitis
- granulomatous, e.g., tuberculosis, sarcoidosis, syphilis
- metabolic, e.g., gout, thyrotoxicosis
- infectious, e.g., S. aureus, S. pneumoniae, P. aeruginosa, herpes zoster
- chemical or physical agents (e.g., thermal, alkali, or acid burns)
- idiopathic

Clinical Features
- severe pain, photophobia, red eye, decreased vision
- pain is best indicator of disease progression
- inflammation of scleral, episcleral, and conjunctival vessels
- may have anterior chamber cells and flare, corneal infiltrate, scleral thinning
- sclera may have a blue hue (best seen in natural light), due to rearranged scleral fibers
- scleral edema or thinning
- failure to blanch with topical phenylephrine

Treatment
- systemic NSAID or steroid (topical steroids are not effective)
- treat underlying etiology

Cornea

- function
  - transmission of light
  - refraction of light (2/3 of total refractive power of eye)
  - barrier against infection, foreign bodies
- transparency due to avascularity, uniform structure and deturgescence (relative dehydration)
- 6 layers (anterior to posterior): epithelium, Bowman’s membrane, stroma, Dua’s layer, Descemet’s membrane, endothelium (dehydrates the cornea; dysfunction leads to corneal edema). A new corneal layer was discovered by H. Dua in 2013 and is characterized as a pre-Descemet’s membrane
- extensive sensory fiber network (V1 distribution); therefore abrasions and inflammation (keratitis) are very painful

Foreign body

- foreign material in or on cornea
- may have associated rust ring if metallic
- patients may note tearing, photophobia, foreign body sensation, red eye
- signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, anterior chamber cells/flare

Complications
- abrasion, infection, scarring, rust ring, secondary iritis

Treatment
- remove under magnification using local anesthetic and sterile needle or refer to ophthalmology (depending on depth and location)
- treat as per corneal abrasion

Corneal Abrasion

- epithelial defect usually due to trauma (e.g., fingernails, paper, twigs), contact lens (Figure 14)

Clinical Features (Table 5)
- pain, redness, tearing, photophobia, foreign body sensation
- de-epithelialized area stains with fluorescein dye
- pain relieved with topical anesthetic

Complications
- infection, ulceration, recurrent erosion, secondary iritis

Treatment
- topical antibiotic (drops or ointment)
- consider topical NSAID (caution due to risk of corneal melt with prolonged use), cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch
- most abrasions clear spontaneously within 24-48 h

Scleromalacia Perforans
- Asymptomatic anterior necrotizing scleritis without inflammation
- Strongly associated with RA
- May result in scleral thinning
- Traumatic perforation can easily occur
  - examine eye very gently

Learn the layers of the cornea
A – Anterior epithelium
B – Bowman’s Membrane
C – Corneal Stroma
D – Dua’s Layer, Descemet’s Membrane
E – Endothelium

A new corneal layer was discovered by H. Dua in 2013 and is characterized as a pre-Descemet’s membrane

Foreign body behind lid may cause multiple vertical corneal epithelial abrasions due to blinking

Topical analgesics should only be used to facilitate examination. They should NEVER be used as treatment for any ocular problem

CEAEDB
Recurrent Erosions

- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

Etiology

- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

Treatment

- as for corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment at bedtime for 3 mo, topical lubrication
- bandage contact lens, anterior stromal puncture or phototherapeutic keratectomy for chronic recurrences

Corneal Ulcer

Etiology

- local necrosis of corneal tissue due to infection
- infection is usually bacterial, rarely viral, fungal, or protozoan (Acanthamoeba)
- secondary to corneal exposure, abrasion, foreign body, contact lens use (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

Clinical Features

- pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- may develop corneal edema, conjunctival injection, anterior chamber cells/flares, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

Complications

- decreased vision, corneal perforation, iritis, endophthalmitis

Investigations

- Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect leaking penetrating lesions; any aqueous leaking will change dark orange dye to bright yellow-green at site of wound

Treatment

- urgent referral to ophthalmology
- culture prior to treatment
- topical antibiotics every hour
- must treat vigorously to avoid complications

Table 5. Corneal Abrasion vs. Corneal Ulcer

<table>
<thead>
<tr>
<th></th>
<th>Abrasion</th>
<th>Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Course</td>
<td>Acute</td>
<td>Subacute (days)</td>
</tr>
<tr>
<td>History of Trauma</td>
<td>Yes</td>
<td>Not usually</td>
</tr>
<tr>
<td>Cornea</td>
<td>Clear</td>
<td>White, necrotic area</td>
</tr>
<tr>
<td>Iris Detail</td>
<td>Clear</td>
<td>Obscured</td>
</tr>
<tr>
<td>Corneal Thickness</td>
<td>Normal</td>
<td>May have crater defect/thinning</td>
</tr>
<tr>
<td>Extent of Lesion</td>
<td>Limited to epithelium</td>
<td>Extension into stroma</td>
</tr>
</tbody>
</table>

Herpes Simplex Keratitis

- usually HSV type 1 (90% of population are carriers)
- may be triggered by stress, fever, sun exposure, immunosuppression

Clinical Features

- pain, tearing, foreign body sensation, red eye, may have decreased vision, eyelid edema
- corneal hypoesthesia
- dendritic (thin and branching) lesion in epithelium that stains with fluorescein
Complications
• corneal scarring (can lead to loss of vision)
• chronic interstitial keratitis due to penetration of virus into stroma
• secondary iritis, secondary glaucoma

Treatment
• topical antiviral such as trifluridine, consider systemic antiviral such as acyclovir
• dendritic debridement
• NO STEROIDS initially – may exacerbate condition
• ophthalmologist must exercise caution if adding topical steroids for chronic keratitis or iritis

Herpes Zoster
• dermatitis of the forehead (CN V1 territory) may involve globe
• Hutchinson’s sign: if tip of nose is involved (nasociliary branch of V1) then eye will be involved in approximately 75% of cases
• if no nasal involvement, eye is involved in 1/3 of patients

Clinical Features
• pain, tearing, photophobia, red eye
• corneal edema, pseudodendrite, SPK
• corneal hypoesthesia

Complications
• corneal keratitis, ulceration, perforation and scarring
• secondary iritis, secondary glaucoma, cataract
• muscle palsies (rare) due to CNS involvement
• occasionally severe post-herpetic neuralgia

Treatment
• oral antiviral (acyclovir, valcyclovir, or famciclovir) immediately
• topical steroids, cycloplegia as indicated for keratitis, iritis
• erythromycin ointment if conjunctival involvement

Keratoconus
• bilateral paracentral thinning and bulging (ectasia) of the cornea to form a conical shape
• usually sporadic, but associated with Down’s syndrome, atopy, contact lens use (theorized to be related to chronic vigorous eye rubbing)
• associated with breaks in Descemet's and Bowman's membrane
• results in irregular astigmatism, scarring, stromal edema

Treatment
• attempt correction with spectacles or contact lens
• cross-linking treatment may halt or slow disease progression
• intrastromal corneal ring segments can help flatten the corneal cone
• penetrating keratoplasty (corneal transplant) 90% successful
• post-operative complications: endophthalmitis, graft rejection, graft failure, graft dehiscence

Arcus Senilis
• hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
• common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
• may be associated with hypercholesterolemia if age <40 yr, check lipid profile
• no associated visual symptoms, no complications, no treatment necessary

Kayser-Fleischer Ring
• brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
• due to deposition of copper pigment in Descemet's membrane
• associated with Wilson's disease
• no associated symptoms or complications of ring
• treat underlying disease

Figure 15. Trigeminal distribution

Steroid treatment for ocular disorders should only be prescribed and supervised by an ophthalmologist, as they can impair corneal healing and exacerbate herpetic keratitis

To detect keratoconus, look for bulging of the lower eyelid when the patient looks downward (Munson’s sign)
The Uveal Tract

- uveal tract (from anterior to posterior) = iris, ciliary body, choroid
- vascularized, pigmented middle layer of the eye, between the sclera and the retina

Uveitis

- uveal inflammation which may involve one, or all three parts of the tract
- idiopathic or associated with autoimmune, infectious, granulomatous, malignant causes
- should be managed by an optometrist or ophthalmologist
- anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis based on primary site of inflammation

Table 6. Anatomic Classification of Uveitis

<table>
<thead>
<tr>
<th>Location</th>
<th>Anterior Uveitis (Iritis)</th>
<th>Intermediate Uveitis</th>
<th>Posterior Uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), both = iridocyclitis</td>
<td>The vitreous is the major site of the inflammation</td>
<td>Inflammation of the choroid and/or retina</td>
</tr>
<tr>
<td>Etiology</td>
<td>Usually idiopathic</td>
<td>Mostly idiopathic, secondary causes include sarcoidosis, Lyme disease, and multiple sclerosis</td>
<td>Bacterial: syphilis, tuberculosis</td>
</tr>
<tr>
<td></td>
<td>Connective tissue diseases (see Rheumatology, RH8)</td>
<td></td>
<td>Viral: herpes simplex virus, CMV in AIDS</td>
</tr>
<tr>
<td></td>
<td>HLA-B27: reactive arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease</td>
<td></td>
<td>Fungal: histoplasmosis, candidiasis</td>
</tr>
<tr>
<td></td>
<td>Non-HLA-B27: juvenile idiopathic arthritis</td>
<td></td>
<td>Parasitic: toxoplasmosis (most common cause), toxocara</td>
</tr>
<tr>
<td></td>
<td>Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster</td>
<td></td>
<td>Immunosuppression may predispose to any of the above infections</td>
</tr>
<tr>
<td></td>
<td>Other: sarcoidosis, trauma, large abrasion, post ocular surgery</td>
<td></td>
<td>Autoimmune: Behçet’s disease (triat of oral ulcers, genital ulcers, and posterior uveitis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Malignancies (masquerade syndrome): metastatic lesions, malignant melanoma</td>
</tr>
</tbody>
</table>

Clinical Features

- Photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased VA (in severe cases with hypopyon), lacrimation
- Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle)
- Anterior chamber “cells” (WBC in anterior chamber due to anterior segment inflammation) and “flare” (protein precipitates in anterior chamber secondary to inflammation), hypopyon (collection of neutrophlic exudates inferiorly in the anterior chamber)
- Occasionally keratic precipitates (clumps of cells on corneal endothelium)
- Iritis typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis, or iritis from herpes simplex and zoster may cause an inflammatory glaucoma (trabeculitis)
- Insidious onset of blurred vision, accompanied by vitreous floaters
- Initial symptoms are usually unilateral but inflammatory changes are usually bilateral and asymmetric
- Associated with anterior uveitis, most severe cases of secondary intermediate uveitis
- Vitreous cells, condensations, and snowballs (vitreous aggregates of inflammatory cells)
- Posterior segment ‘snowbank’ = gray-white fibrovascular plaque at the pars plana

Complications

- Inflammatory glaucoma
- Posterior synechiae
  - Adhesions of posterior iris to anterior lens capsule
  - Indicated by an irregularly shaped pupil
  - If occurs 360°, entraps aqueous in posterior chamber, iris bows forward “iris bombé” → angle closure glaucoma
- Peripheral anterior synechiae (rare): adhesions of iris to cornea → secondary angle closure glaucoma
- Cataracts
- Band keratopathy (with chronic iritis)
- Superficial corneal calcification keratopathy
- Macular edema with chronic iritis

Treatment

- Mydriatics: dilate pupil to prevent formation of posterior synechiae and to decrease pain from ciliary spasm
- Steroids: topical, sub-tenon, or systemic
- Systemic analgesia
- Extensive medical workup may be indicated to rule out secondary causes
- Systemic or sub-tenon/intravitreal steroids and immunosuppressive agents
- Vitrectomy, cryotherapy, or laser photocoagulation to the “snowbank”
- Steroids: sub-tenon, intravitreal, or systemic if indicated (e.g. threat of vision loss)
**Lens**

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

**Cataracts**

- any opacity of the lens, regardless of etiology
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, posterior subcapsular

**Etiology**

- acquired
  - age-related (over 90% of all cataracts)
  - cataract associated with systemic disease (may have juvenile onset)
    - DM
    - metabolic disorders (e.g. Wilson's disease, galactosemia, homocystinuria)
    - hypocalcemia
  - traumatic (may be rosette shaped)
  - intraocular inflammation (e.g. uveitis)
  - toxic (steroids, phenothiazines)
  - radiation
- congenital
  - high myopia
  - present with altered red reflex or leukocoria
  - treat promptly to prevent amblyopia

**Clinical Features**

- gradual, painless, progressive decrease in VA
- glare, dimness, halos around lights at night, monocular diplopia
- "second sight" phenomenon; patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
  - patient may read without previously needed reading glasses
- diagnose by slit-lamp exam, and by noting changes in red reflex using ophthalmoscope
- may impair view of retina during fundoscopy

**Treatment**

- medical: attempt correction of refractive error, no strong evidence suggesting benefit of vitamin supplementation
- surgical: definitive treatment
  - indications for surgery
    - to improve visual function in patients whose visual loss leads to functional impairment (no need to wait for "ripe" cataract, may postpone surgery as long as one eye has sufficient vision)
    - to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
    - congenital or traumatic cataracts
    - phacoemulsification (phaco = lens)
  - most commonly used surgical technique (see Surgical Ophthalmology, OP44)
  - post-operative complications
    - RD, endophthalmitis, dislocated IOL, macular edema, glaucoma
    - with new foldable IOLs that have truncated edges, <10% of patients get posterior capsular opacification, which should be treated with YAG laser

**Prognosis**

- excellent if not complicated by other ocular disease

**Dislocated Lens (Ectopia Lentis)**

**Etiology**

- associated with Marfan's Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic
Clinical Features
• decreased VA
• may get unilateral diplopia
• iridodenesis (quivering of iris with movement)
• direct ophthalmoscopy may elicit abnormal red reflex

Complications
• cataract, glaucoma, uveitis

Treatment
• surgical correction ± lens replacement

Vitreous
• clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
• normally adherent to optic disc, pars plana, and along major retinal blood vessels

Posterior Vitreous Detachment

Etiology
• central vitreous commonly shrinks and liquefies with age (syneresis)
• during syneresis, molecules that hold water condense causing vitreous floaters
• liquid vitreous moves between posterior vitreous gel and retina
• vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

Clinical Features
• floaters, flashes of light

Complications
• traction at areas of abnormal vitreoretinal adhesions may cause retinal tears/detachment
• retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
• complications more common in high myopes and following ocular trauma (blunt or perforating)

Treatment
• acute onset of PVD requires a dilated fundus exam to rule out retinal tears/detachment
• no specific treatment available for floaters/flashes of light

Vitreous Hemorrhage

• bleeding into the vitreous cavity

Etiology
• PDR
• retinal tear/detachment
• PVD
• retinal vein occlusion
• trauma

Clinical Features
• sudden loss of VA
• may be preceded by many floaters and/or flashes of light
• ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

Treatment
• ultrasound (B-scan) to rule out RD
• expectant: in non-urgent cases (e.g. no DRt), blood usually resorbs in 3-6 mo
• surgical: vitrectomy ± RD repair ± retinal endolaser to possible bleeding sites/vessels

Any time a vitreous or retinal hemorrhage is seen in a child, must rule out child abuse
Endophthalmitis and Vitritis

• intraocular infection: acute, subacute, or chronic

Etiology
• most commonly a post-operative complication; risk following cataract surgery is <0.1%
• also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
• etiology usually bacterial, may be fungal

Clinical Features
• painful, red eye, photophobia, discharge
• severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
• may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased IOP, etc.)

Treatment (see Ocular Trauma, OP42)
• OCULAR EMERGENCY: presenting vision best indicates prognosis
• LP or worse: admission, immediate vitrectomy, and intravitreal antibiotics to prevent loss of vision
• HM or better: vitreous tap for culture and intravitreal antibiotics
• topical fortified antibiotics

Retina

• composed of two parts (Figure 2)
  ▪ neurosensory retina: comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
  ▪ retinal pigmented epithelium (RPE) layer: external to neurosensory retina
• macula: rich in cones (for color vision); most sensitive area of retina; looks darker due to increase luteal pigment, lack of retinal vessels, and thinning of retina in this region; 15° temporal and slightly below the optic disc
• fovea: center of macula; responsible for acute, fine vision
• optic disc: slightly oval vertically, pinkish color with centrally depressed yellow cup (normal C:D is <0.5), retinal artery and vein pass through cup
• ora serrata: irregularly-shaped, anterior margin of the retina (can only be visualized with indirect ophthalmoscopy of the far peripheral retina, or through a Goldmann 3 mirror lens)

Central Retinal Artery Occlusion

Etiology
• emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
• thrombus
• temporal arteritis

Clinical Features
• sudden, painless (except in GCA), severe monocular loss of vision
• RAPD
• patient may have experienced transient episodes in the past (amaurosis fugax)
• fundoscopy
  ▪ “cherry-red spot”
  ▪ retinal pallor
  ▪ narrowed arterioles, boxcarring (segmentation of blood in arteries)
  ▪ cotton wool spots (retinal infarcts)
  ▪ cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations
  ▪ after ~6wk cherry-red spot recedes and optic disc pallor becomes evident

Treatment
• OCULAR EMERGENCY: attempt to restore blood flow within 2 h
  ▪ the sooner the treatment = better prognosis (irreversible retinal damage if >90 min of complete CRAO)
  ▪ massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
  ▪ decrease IOP
    ▪ topical β-blockers
    ▪ inhaled oxygen-carbon dioxide mixture
    ▪ IV acetazolamide
    ▪ severe = mannitol (draws fluid from eye)
    ▪ drain aqueous fluid – anterior chamber paracentesis (carries risk of endophthalmitis)
  ▪ treat underlying cause to prevent CRAO in other eye

Remember to inquire about tetanus status in post-traumatic endophthalmitis

Hallmark of CRAO
“Cherry-red spot” located at center of macula (visualization of unaffected highly vascular choroid through the thin fovea)

Treatment for a central retinal artery occlusion (CRAO) must be initiated within 2 h of symptom onset for any hope of restoring vision
Branch Retinal Artery Occlusion

- only part of the retina becomes ischemic resulting in a visual field loss
- more likely to be of embolic etiology than CRAO; need to search for source
- management: ocular massage to dislodge embolus if VA is affected

Central/Branch Retinal Vein Occlusion

- second most frequent “vascular” retinal disorder after DR
- usually a manifestation of a systemic disease (e.g. HTN, DM)
- thrombus occurs within the lumen of the blood vessel

Predisposing Factors
- arteriosclerotic vascular disease
- HTN
- DM
- glaucoma
- hyperviscosity (e.g. polycythemia rubra vera, sickle-cell disease, lymphoma, leukemia)
- drugs (e.g. oral contraceptive pill, diuretics)

Clinical Features
- painless, monocular, gradual or sudden visual loss
- ± RAPD
- fundoscopy
  - “blood and thunder” appearance
  - diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - no RAPD, VA approximately 20/80
    - mild hemorrhage, few cotton wool spots
    - resolves spontaneously over weeks to months
    - may regain normal vision if macula intact
  - hemorrhagic/ischemic retinopathy
    - usually older patient with deficient arterial supply
    - RAPD, VA approximately 20/200, reduced peripheral vision
    - more hemorrhages, cotton wool spots, congestion
    - poor visual prognosis

Complications
- degeneration of RPE
- neovascularization of retina and iris (secondary rubeosis), leading to secondary glaucoma
- vitreous hemorrhage
- macular edema

Treatment
- no treatment available to restore vision in CRVO/BRVO
- treat underlying cause/contributing factor
- fluorescein angiography to determine extent of retinal non-perfusion (risk of neovascularization)
- retinal laser photocoagulation, or intravitreal anti-VEGF injection to reduce retinal or iris neovascularization and prevent neovascular glaucoma
- macular grid laser photocoagulation for the treatment of macular edema in BRVO, not CRVO, intravitreal or slow-release biodegradable corticosteroid, or anti-VEGF injection is effective in the treatment of macular edema in both CRVO and BRVO

Retinal Detachment

- cleavage in the plane between the neurosensory retina and the RPE
- three types
  - rhegmatogenous (most common)
    - caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - tears may be caused by PVD, degenerative retinal changes, trauma, or iatrogenically
    - incidence increases with advancing age, in high myopes, and after ocular surgery/trauma
  - tractional
    - caused by traction (due to vitreal, epiretinal, or subretinal membrane) pulling the neurosensory retina away from the underlying RPE
    - found in conditions such as DR, CRVO, sickle cell disease, ROP, and ocular trauma
  - exudative
    - caused by damage to the RPE resulting in fluid accumulation in the subretinal space
    - main causes are intraocular tumors, posterior uveitis, central serous retinopathy

Efficacy and Safety of Widely Used Treatments for Macular Edema Secondary to Retinal Vein Occlusion: A Systematic Review

Purpose: To assess the efficacy of widely used treatments for macular edema (MO) secondary to retinal vein occlusion (RVO). MO secondary to RVO can cause vision loss due to blockage of the central retinal vein (CRVO) or a branch retinal vein (BRVO).

Outcomes: Mean change in best corrected visual acuity (BCVA) from baseline and/or number of patients gaining at least 10 letters from baseline to 6 months or equivalent time point.

Results: 14 unique RCTs identified. Ranibizumab 0.5 mg produced greater improvements in BCVA at 6 mo compared to sham in BRVO (mean difference 11 letters; 95% CI 7.03-14.17) and CRVO (mean difference 14 letters; 95% CI 10.51-17.69). Improvements in BCVA were also observed with dexamethasone intravitreal implant (IVT) 0.7 mg compared with sham in patients with BRVO or CRVO (mean difference 2.9 letters; 95% CI 0.7-4.3). The difference was significant with BRVO alone, but not CRVO alone. At 16 mo in a large prospective RCT, a greater proportion of patients with BRVO gained >15 letters with laser therapy vs. no treatment (OR 3.16; 95% CI 1.25-8.00), whereas no difference was observed in a 9 mo end point smaller study. Three studies showed no benefit for laser therapy in CRVO.

Conclusions: Both ranibizumab and dexamethasone IVT show significant improvements over previously accepted standard of care (laser therapy) for the treatment of BRVO and CRVO.

The “blood and thunder” appearance on fundoscopy is very characteristic of a CRVO

There is an 8-10% risk of developing CRVO or BRVO in other eye

GENEVA Phase 3 Trials in BRVO and CRVO

Ophthalmology 2010;17:1134-1146

Randomized sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion.

Dexamethasone intravitreal implant reduces the risk of vision loss and improves the speed and incidence of visual improvement in eyes with macular edema 2° to BRVO and CRVO.

Superotemporal retina is the most common site for horseshoe tears
Clinical Features
- sudden onset
- flashes of light
  - due to mechanical stimulation of the retinal photoreceptors
- floaters
  - hazy spots in the line of vision which move with eye position, due to drops of blood from torn vessels bleeding into the vitreous
- curtain of blackness/peripheral field loss
  - darkness in one field of vision when the retina detaches in that area
- loss of central vision (if macula "off")
- decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
- ophthalmoscopy: detached retina is gray-white with surface blood vessels, loss of red reflex
  - ± RAPD
- x-ray of visual recovery varies inversely with the amount of time the retina is detached and
- loss of vision, vitreous hemorrhage, recurrent RD

Complications
- loss of vision, vitreous hemorrhage, recurrent RD
- a RD is an emergency, especially if the macula is still attached (macula "on")
- prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

Retinitis Pigmentosa
- worldwide incidence between 1/3,500 and 1/7,000 people
- many forms of inheritance, most commonly autosomal recessive (60%)
- hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy

Clinical Features
- night blindness, decreased peripheral vision ("tunnel vision"), decreased central vision (macular changes), glare (from cataract)

Investigations
- fundoscopy: areas of "bone-spicule" pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
- electrophysiological tests: electoretinography (ERG) and electrooculography (EOG) assist in diagnosis

Treatment
- no treatments available to reverse the condition; cataract extraction improves visual function; vitamin A and vitamin E supplementation can reduce progression of disease in some patients

Leber’s Congenital Amaurosis
- worldwide incidence 1/80,000
- inherited degeneration, autosomal recessive
- symptoms: resting nystagmus, sluggish or no papillary response, severe vision loss/blindness
- diagnosis: 11 types, confirmed by genetic testing
- management: no treatments available to reverse the conditions for most forms; one form (LCA2) shown to be successfully treatable by gene replacement using adeno-associated virus

Clinical Features
- management: no treatments available to reverse the conditions for most forms; one form (LCA2) shown to be successfully treatable by gene replacement using adeno-associated virus

Vitamin A and Fish Oils for Retinitis Pigmentosa
Purpose: To determine the efficacy and safety of vitamin A and fish oils (docosahexaenoic acid (DHA)) in preventing the progression of RP
Selection Criteria: RCTs evaluating the effectiveness of vitamin, fish oils, or both as a treatment for RP
Results: 3 RCTs with 866 participants. No toxicity or adverse events reported. A trial reported a statistically significant benefit of vitamin supplementation on the progression of visual field loss or visual acuity loss. 2 of 3 trials reported a statistically significant difference in ERG amplitudes among some subgroups, but these findings have not been replicated or substantiated in other trials
Conclusions: There is no clear evidence for benefit of treatment with vitamin A and/or DHA for RP when measuring mean change in visual fields and ERG amplitudes at one year and the mean change in visual acuity at 5 yr follow-up.

Age-Dependent Effects of Gene Therapy for Leber’s Congenital Amaurosis: A Phase 1 Dose-Escalation Trial
Lancet 2009;374:1597-1605
Objective: To evaluate the effect of gene therapy on retinal and visual function among patients with Leber’s congenital amaurosis.
Methods: Phase 1 trial. Patients aged 8-44 (n=12) with RPE65-associated Leber’s congenital amaurosis received a single subretinal injection of adeno-associated virus (AAV) containing the gene encoding the protein needed for isomerohydrolase (RPE65) (AAV2-hRPE65v2) in the worst eye at low, medium, or high dose. Patients were assessed before and after injections. Outcomes were subjective and objective measures of vision.
Results: AAV2-hRPE65v2 was tolerated. No serious adverse events were recorded. Visual improvement was noted for all patients. All patients reported improved vision in dimly lit environments. Visual fields improved in all patients. Pupillary light responses were increased by at least 2 log unit for all patients. Greatest visual improvement was noted in children.
Conclusion: AAV2-hRPE65v2 is safe and improves vision among patients with Leber’s congenital amaurosis.

Essential Med Notes 2015 Retina Ophthalmology OP25
Age-Related Macular Degeneration

- leading cause of irreversible blindness in the western world, associated with increasing age, usually bilateral
- 10% of people >65 yr old have some degree of AMD
- F>M
- degenerative changes are concentrated at the macula, thus only central vision is lost; peripheral vision (important for navigation) is maintained so patients can usually maintain an independent lifestyle

Classification
- Non-Exudative/“Dry” (Non-Neovascular) AMD
  - most common type of AMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow-white deposits between the RPE and Bruch’s membrane (area separating inner choroidal vessels from RPE)
  - RPE atrophy: coalescence of depigmented RPE, clumps of focal hyperpigmentation, or hypopigmentation
  - may progress to neovascular AMD

- Exudative/“Wet” (Neovascular) AMD
  - 10% of AMD, but 80% of AMD that results in severe visual loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch’s membrane causing subsequent growth and proliferation of choroidal capillaries
  - may lead to serous detachment of overlying RPE and retina, hemorrhage and lipid precipitates into subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of hemorrhagic RD leads to disciform scarring and severe central visual loss

Risk Factors
- female
- increased age
- family history
- smoking
- Caucasian race
- blue irides

Clinical Features
- variable degree of progressive central visual loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

Investigations
- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography: assess the type and location of the choroidal neovascularization – pathologic new vessels leak dye

Treatment
- non-neovascular “dry” AMD
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed-circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visors
  - see Age-related Eye Disease Study (AREDS)
- neovascular “wet” AMD
  - see Common Medications, OP44
  - laser photocoagulation for neovascularization
  - 50% of choroidal neovascularization cannot be treated initially
  - no definitive treatment for disciform scarring
  - PDT with verteporfin (Visudyne®)
    - IV injection of verteporfin followed by low intensity laser to area of choroidal neovascularization
  - intravitreal injection of anti-VEGF
    - pegaptanib (Macugen®), ranibizumab (Lucentis®), bevacizumab (Avastin®) (see VEGF Inhibitors, OP45)

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Glaucoma

Definition
- progressive optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

Background
- aqueous is produced by the ciliary body and flows from the posterior chamber to the anterior chamber through the pupil, and drains into the episcleral veins via the trabecular meshwork and the Canal of Schlemm
- an isolated increase in IOP is termed OHT (or glaucoma suspect) and these patients should be followed for increased risk of developing glaucoma (10% if IOP 20-30 mmHg; 40% if IOP 30-40 mmHg; and most if IOP >40 mmHg)
- pressures >21 mmHg are more likely to be associated with glaucoma; however, up to 50% of patients with glaucoma do not have IOP >21 mmHg
- loss of peripheral vision most commonly precedes central loss
- sequence of events: gradual pressure rise → increased C:D ratio → visual field loss

Investigations
- medical and family history
- VA testing
- slit-lamp exam to assess anterior chamber depth
- ophthalmoscopy to assess the disc features
- tonometry by applanation or indentation to measure IOP
- perimetry to measure corneal thickness
- future follow-up includes optic disc examination, IOP measurement, and visual field testing to monitor course of disease

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Average IOP = 15 ± 3 mmHg
- Normal C:D ≤ 0.4
- Suspect glaucoma if C:D ratio >0.6, C:D ratio between eyes >0.2, or cup approaches disc margin

Figure 19. Glaucomatous damage

Figure 20. Aqueous flow and sites of potential resistance

Ten Year Follow-Up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study: AREDS Report No. 36
Study: Randomized clinical trial.
Objective: To describe 10 year progression rates to intermediate or advanced AMD.
Participants: Age-related eye disease study (AREDS) participants were observed for an additional 5 years after RCT completion. Participants aged 55-80 yr with no AMD or AMD of varying severity (n=4,757) were followed up in the AREDS trial for a median duration of 6.5 yr. When the trial ended, 3,349 of the 4,203 surviving participants were followed for 5 additional yr.
Intervention: Treatment with antioxidant vitamins and minerals.
Main Outcome: Development of varying stages of AMD and changes in visual acuity.
Results: The risk of progression to advanced AMD increased with increasing age (p=0.01) and severity of drusen. Women (p=0.005) and current smokers (p<0.001) were at increased risk of neovascular AMD. In the oldest participants with the most severe AMD status at baseline, the risks of developing neovascular AMD and central geographic atrophy by 10 yr were 48.1% and 26.0%, respectively. Similarly, rates of progression to large drusen increased with increasing severity of drusen at baseline, with 70.9% of participants with bilateral medium drusen progressing to large drusen and 13.8% to advanced AMD in 10 yr. Median visual acuity at 10 yr in eyes that had large drusen at baseline but never developed advanced AMD was 20/20; eyes that developed advanced AMD had a median visual acuity of 20/200.
Conclusion: The natural history of AMD demonstrates relentless loss of vision in persons who developed advanced AMD.
Primary Open-Angle Glaucoma

- most common form, >95% of all glaucoma cases
- due to obstruction of aqueous drainage within the trabecular meshwork and its drainage into the Canal of Schlemm
- insidious and asymptomatic, screening is critical for early detection

Major Risk Factors

- elevated IOP (>21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic

Minor Risk Factors

- myopia
- HTN
- DM
- hyperthyroidism (Graves’ disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 wk of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

Clinical Features

- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased C:D ratio (vertical C:D >0.6)
  - significant C:D asymmetry between eyes (>0.2 difference)
  - thinning, notching of the neuroretinal rim
  - flame shaped disc hemorrhage
  - 360º of peripapillary atrophy
  - nerve fiber layer defect
  - large vessels become nasally displaced
- visual field loss
  - slow, progressive, irreversible loss of peripheral vision
  - paracentral defects, arcuate scotoma, and nasal step are characteristics (see Figure 19)
  - late loss of central vision if untreated

Treatment

- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see Glaucoma Medications, Table 12, OP45)
  - topical cholinergics
  - topical prostaglandin analogues
  - topical α-adrenergics
  - decrease aqueous production
    - topical β-blockers
    - topical and oral carbonic anhydrase inhibitor
    - topical α-adrenergics
  - laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
  - trabeculectomy (see Surgical Ophthalmology, OP44)
  - serial optic nerve head examinations, IOP measurements, and visual field testing to monitor disease course

Normal Tension Glaucoma

- POAG with IOP in normal range
- often found in women >60 but may occur earlier
- damage to optic nerve may be due to vascular insufficiency

Treatment

- treat reversible causes
Secondary Open Angle Glaucoma

- increased IOP secondary to ocular/systemic disorders that obstruct the trabecular meshwork
  - steroid-induced glaucoma
  - traumatic glaucoma
  - pigmentary dispersion syndrome
  - pseudoexfoliation syndrome

Primary Angle-Closure Glaucoma

- 5% of all glaucoma cases
- peripheral iris bows forward in an already susceptible eye with a shallow anterior chamber obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block, and results in inability of the aqueous to flow from the posterior chamber to the anterior chamber resulting in a sudden rise in IOP

Risk Factors
- hyperopia: small eye, big lens – large lens crowds the angle
- age >70 yr
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

Clinical Features
- red, painful eye = RED FLAG
- unilateral, but other eye increased risk
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- corneal edema with conjunctival injection
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

Complications
- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae, resulting in permanent angle closure

Treatment
- OCULAR EMERGENCY: refer to ophthalmologist for acute angle closure glaucoma
  - laser iridotomy
  - aqueous suppressants and hyperosmotic agents
- medical treatment (see Glaucoma Medications. Table 12, OP45)
  - miotic drops (pilocarpine) to reverse pupillary block
  - decrease IOP
    - topical β-blockers
    - topical adrenergics
    - topical cholinergics
    - pilocarpine 1-4% q15min, up to q5min
    - systemic carbonic anhydrase inhibitors
      - IV acetazolamide 250-500 mg
    - systemic hyperosmotic agents
      - oral glycerine 1 g/kg
      - IV mannitol 1 g/kg

Secondary Angle-Closure Glaucoma

Uveitis
- inflamed iris adheres to lens (posterior synechiae)

Neovascular Glaucoma
- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with PDR or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris vessels
Pupils

- pupil size is determined by the balance between the sphincter muscle and the dilator muscle
- sphincter muscle is innervated by the parasympathetic nervous system
  - carried by CN III: pre- and post-ganglionic fibers synapse in ciliary ganglion, and use acetylcholine as the neurotransmitter
- dilator muscle is innervated by the sympathetic nervous system (SNS)
  - first order neuron = hypothalamus → brainstem → spinal cord
  - second order/preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
  - third order/postganglionic fibers originate in the superior cervical ganglion, neurotransmitter is noradrenaline
    - as a diagnostic test, 4-10% cocaine prevents the re-uptake of noradrenaline, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner's Syndrome)
    - see Neurology, Figure 8, N6

Pupillary Light Reflex

- light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → bilateral midbrain
- impulses enter bilaterally in midbrain via pretectal area and Edinger-Westphal nuclei
- nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes

Pupil Abnormalities

Denervation Hypersensitivity

- when post-ganglionic fibers are damaged, the understimulated end-organ develops an excess of neuroreceptors and becomes hypersensitive
- postganglionic parasympathetic lesions (i.e. Adie's pupil)
  - pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
- postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner's syndrome)
  - pupil will dilate with 0.125% adrenaline, normal pupil will not

Local Disorders of Iris

- posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
- ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o'clock positions resulting in a vertically oval pupil that reacts poorly to light
- trauma (e.g. post-intraocular surgery)

Anisocoria

- unequal pupil size
- idiopathic/physiologic anisocoria
  - 20% of population
  - round, regular, <1 mm difference
  - pupils reactive to light and accommodation
  - responds normally to mydriatics/miotics
- post eye surgery
- see Table 7 for other causes of anisocoria
Figure 22. Approach to anisocoria
Reproduced with permission from: Kedar S, Biousse V, Newman NJ. Approach to the patient with anisocoria. In: UpToDate, Rose, BD (editor), UpToDate, Waltham, MA, 2011. Copyright 2011 UpToDate, Inc. For more information visit www.uptodate.com

Table 7. Summary of Conditions Causing Anisocoria

<table>
<thead>
<tr>
<th>Features</th>
<th>Site of Lesion</th>
<th>Light and Accommodation</th>
<th>Anisocoria</th>
<th>Mydriatics/Miotics</th>
<th>Effect of Pilocarpine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABNORMAL MIOTIC PUPIL</strong> (impaired pupillary dilation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argyll-Robertson Pupil</td>
<td>Irregular, usually bilateral</td>
<td>Midbrain</td>
<td>Poor in light; better to accommodation</td>
<td>Dilates/Constricts</td>
<td></td>
</tr>
<tr>
<td>Horner’s Syndrome</td>
<td>Round, unilateral, ptosis, anhidrosis, pseudonephphalamos</td>
<td>Sympathetic system</td>
<td>Both brisk</td>
<td>Greater in dark</td>
<td>Dilates/Constricts</td>
</tr>
</tbody>
</table>

| **ABNORMAL MYDRIATIC PUPIL** (impaired pupillary constriction) |
| Adie’s Tonic Pupil | Irregular, larger in bright light | Ciliary ganglion | Poor in light, better to accommodation | Greater in light | Dilates/Constricts | Constricts (hypersensitivity to dilute pilocarpine) |
| CN III Palsy | Round | Superficial CN III | ± fixed (acutely) at 7-8 mm | Greater in light | Dilates/Constricts | Constricts |
| Mydriatic Pupil | Round, uni- or bilateral | Iris sphincter | Fixed at 7-8 mm | Greater in light | No effect | Will not constrict |
Dilated Pupil (Mydriasis)

**Sympathetic Stimulation**
- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

**Parasympathetic Understimulation**
- cyclopentolate/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, DM (may spare pupil), trauma
  - CN III palsy will respond to drugs (e.g. pilocarpine), unlike a pupil dilated from medication (mydriatics)

**Acute Angle-Closure Glaucoma**
- fixed, mid-dilated pupil

**Adie's Tonic Pupil**
- 80% unilateral, F>M
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- if decreased deep tendon reflexes may be Adie's syndrome
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
  - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- long-standing Adie's pupils are smaller than unaffected eye

**Trauma**
- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit-lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

Constricted Pupil (Miosis)

**Senile Miosis**
- decreased sympathetic stimulation with age

**Parasympathetic Stimulation**
- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - cholinesterase inhibitor: phospholine iodide
  - opiates, barbiturates

**Horner's Syndrome**
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis, anhydrosis of ipsilateral face/neck
- application of cocaine 4-10% (blocks reuptake of noradrenaline) to eye does not result in pupil dilation (vs. physiologic anisocoria), therefore confirms diagnosis
- hydroxyamphetamine 1% (stimulates noradrenaline release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- postganglionic lesions result in denervation hypersensitivity, which will cause pupil to dilate with 0.125% adrenaline, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumor, Pancoast tumor, goiter, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabes dorsalis, cervical vertebral fractures

**Iritis**
- miotic pupil initially
- later, may be irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light
Argyll-Robertson Pupil
- both pupils irregular and <3 mm in diameter, ± ptosis
- does not respond to light stimulation
- responds to accommodation (light-near dissociation)
- suggestive of neurosyphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)

Other Causes
- optic neuritis, retinal lesions

Relative Afferent Pupillary Defect

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light, caused by a lesion in visual afferent (sensory) pathway anterior to optic chiasm
- differential diagnosis: large RD, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, optic neuritis (most common)
- does not occur with media opacity (e.g. corneal edema, cataracts)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffected eye to the affected eye, “paradoxical” dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides
- if the defect is bilateral there is no RAPD, as dilation is measured relative to the other eye
Malignancies

- uncommon site for 1° malignancies
- eye usually affected secondarily by cancer or cancer treatments
- see Retinoblastoma, OP41

Lid Carcinoma

Etiology
- basal cell carcinoma (rodent ulcer) (90%)
  - spread via local invasion, rarely metastasizes
  - ulcerated center, indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
  - spread via local invasion, may also spread to nodes and metastasize
  - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
  - often masquerades as chronic blepharitis or recurrent chalazion
  - highly invasive, metastasize
- Kaposi’s sarcoma, malignant melanoma, Merkel cell tumor, metastatic tumor

Treatment
- incisional or excisional biopsies
- may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
- surgical reconstruction

Malignant Melanoma

- most common 1° intraocular malignancy in adults
- more prevalent in Caucasians
- arise from uveal tract, 90% choroidal melanoma
- hepatic metastases predominate

Treatment
- imaging to investigate spread
- depending on the size of the tumor, either radiotherapy, enucleation, limited surgery

Metastases

- most common intraocular malignancy in adults
- most commonly from breast and lung in adults, neuroblastoma in children
- usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
- may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

Treatment
- local radiation, chemotherapy
- enucleation if blind, painful eye

Ocular Manifestations of Systemic Disease

HIV/AIDS

- up to 75% of patients with AIDS have ocular manifestations

External Ocular Signs
- Kaposi’s sarcoma
  - secondary to human herpes virus 8 (HHV-8), affects conjunctiva of lid or globe
  - numerous vascular skin malignancies
  - differential diagnosis: subconjunctival hemorrhage (non-clearing), hemangioma
- multiple molluscum contagiosum
- herpes simplex keratitis
- herpes zoster keratitis
Retina
- HIV retinopathy (most common)
  - cotton wool spots in >50% of HIV patients
  - intraretinal hemorrhage
- CMV retinitis
  - ocular opportunistic infection that develops in late stages of HIV when severely immunocompromised (CD4 count ≤50)
  - a necrotizing retinitis, with retinal hemorrhage and vasculitis, "brushfire" or "pizza pie" appearance
  - presents with scotomas (macular involvement and RD, blurred vision, and floaters)
  - untreated infection will progress to other eye in 4-6 wk
  - treatment: virostatic agents (e.g. gancyclovir or foscarnet) via IV or intravitreal injection
- necrotizing retinitis
  - from herpes simplex virus, herpes zoster, toxoplasmosis
- disseminated choroiditis
  - *Pneumocystis carinii*, *Mycobacterium avium intracellulare*, *Candida*

Other Systemic Infections
- herpes zoster
  - see *Herpes Zoster*, OP19
- candidal endophthalmitis
  - fluffy, white-yellow, superficial retinal infiltrate that may eventually result in vitritis
  - may present with inflammation of the anterior chamber
  - treatment: systemic amphotericin B, oral fluconazole
- toxoplasmosis
  - focal, gray-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous infiltration (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by *Toxoplasma gondii* protozoa transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folinic acid, or clindamycin. Consider adding steroids if severe inflammation (vitritis, macular or optic nerve involvement)

Diabetes Mellitus
- see *Endocrinology*, E6
- most common cause of blindness in young people in North America
- consider DM if unexplained retinopathy, cataract, extraocular muscle palsy, optic neuropathy, sudden change in refractive error
- loss of vision due to
  - progressive microangiopathy leading to macular edema
  - progressive DR → neovascularization → traction → RD and vitreous hemorrhage
  - rubecosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

DIABETIC RETINOPATHY

Background
- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening of basement membrane)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

Classification
- non-proliferative: increased vascular permeability and retinal ischemia
  - microaneurysms
  - dot and blot hemorrhages
  - hard exudates (lipid deposits), non-specific for DR
  - macular edema
- advanced non-proliferative (or pre-proliferative)
  - non-proliferative findings plus
  - venous beading (in ≥2 of 4 retinal quadrants)
  - intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
    - IRMA: dilated, leaky vessels within the retina
  - cotton wool spots (nerve fiber layer infarcts)
- proliferative
  - 5% of patients with DM will reach this stage

Macular edema is the most common cause of visual loss in patients with background DR

Presence of DR in:
Type 1 DM
- 25% after 5 yr
- 80% after 10 yr
- >80% after 15 yr
Type 2 DM
- 20% at time of diagnosis
- 80% after 20 yr

Expanded 2 Year Follow-Up of Ranibizumab Plus Prompt or Deferred Laser or Triamcinolone Plus Prompt Laser for Diabetic Macular Edema
*Ophthalmology* 2011;118:609-614
Ranibizumab (Lucentis®) with prompt or deferred laser is more effective than intravitreal corticosteroid injections + laser or laser alone with sustained efficacy up to 24 mo.
- neovascularization of iris, disc, retina to vitreous
- neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
- vitreous hemorrhage from bleeding, fragile new vessels, fibrous tissue can contract causing tractional RD
- high risk of severe visual loss secondary to vitreous hemorrhage, RD

Screening Guidelines for Diabetic Retinopathy
- type 1 DM
  - screen for retinopathy beginning annually 5 yr after disease onset
  - annual screening indicated for all patients over 12 yr and/or entering puberty
- type 2 DM
  - initial examination at time of diagnosis, then annually
- pregnancy
  - oculomotor exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
- gestational diabetics are not at risk for DR

Optic Neuropathy
- visual acuity loss due to infarction of optic disc/nerve
- usually recover within few months
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- usually CN III infarct

Extraocular Muscle Palsy
- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- may involve CN IV and VI
- usually recover within few months

Optic Neuropathy
- visual acuity loss due to infarction of optic disc/nerve

Hypertension Retinopathy
- can be considered for eyes with clinically significant macular edema

Figure 25. DM vs. HTN retinopathy

**Clinical significance:**
- macular edema is defined as thickening of the retina at or within 500 µm of the center of the macula

**Effects of Medical Therapies on Retinopathy**

**Progression in Type 2 DM**

<table>
<thead>
<tr>
<th>Method</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive glycemic control, combination therapy for dyslipidemia, and intensive blood-pressure control may limit the progression of DR in persons with type 2 DM.</td>
<td>Rates of progression of DR at 4 yr were 7.3% with intensive glycemia therapy vs. 10.4% with standard therapy (OR 0.79; 95% CI 0.61-0.97).</td>
<td>Intensive glycemic control and intensive combination treatment of dyslipidemia may limit the progression of DR in persons with type 2 DM.</td>
</tr>
</tbody>
</table>

**Early Treatment Diabetic Retinopathy Study (ETDRS)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Objectives</th>
<th>Patients</th>
<th>Intervention</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized clinical trial.</td>
<td>Participants with type 2 DM, between the ages of 18 and 70 yr with moderate or severe nonproliferative DR or mild PDR in both eyes, with no previous photocoagulation treatment, and with visual acuity of 20/40 or better (20/200 or better if macular edema is present) were eligible for this study.</td>
<td>To evaluate argon laser photocoagulation and aspirin treatment in the management of patients with nonproliferative or early PDR.</td>
<td>Men and women between the ages of 18 and 70 yr with moderate or severe nonproliferative DR or mild PDR in both eyes, with no previous photocoagulation treatment, and with visual acuity of 20/40 or better (20/200 or better if macular edema is present) were eligible for this study.</td>
<td>All study patients had one eye randomly assigned to immediate photocoagulation and the other eye to deferral of photocoagulation until high-risk proliferative retinopathy developed.</td>
<td>A total of 3,711 patients were recruited to follow a minimum of 4 yr to provide long-term information on the risks and benefits of the treatments under study. The study demonstrated that focal photocoagulation for macular edema reduces the risk of moderate visual loss and should be considered for eyes with clinically significant macular edema. Scatter photocoagulation reduces the risk of severe visual loss. The ETDRS does not support scatter treatment before the severe nonproliferative stage of DR. Aspirin treatment (850 mg/day) does not alter progression of DR.</td>
<td>Before current treatments, the progression for patients with PDR was blindness within 5 yr for &gt;50% of patients. Rates of blindness in ETDRS patients following the development of proliferative retinopathy are remarkably lower.</td>
</tr>
</tbody>
</table>
Hypertension

- retinopathy is the most common ocular manifestation
- chronic HTN retinopathy: arteriovenous (AV) nicking, blot retinal hemorrhages, microaneurysms, cotton wool spots
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema

Table 8. Keith-Wagener-Barker Classification

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Mild arterial narrowing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Obvious arterial narrowing with focal irregularities</td>
</tr>
<tr>
<td>Group 3</td>
<td>Group 2 characteristics plus: Cotton wool spots Hemorrhage and/or exudate</td>
</tr>
<tr>
<td>Group 4</td>
<td>Group 3 plus papilledema</td>
</tr>
</tbody>
</table>

Multiple Sclerosis

- see Neurology, N52

Clinical Features

- blurred vision and decreased color vision: secondary to optic neuritis
- central scotoma: due to damage to papillomacular bundle of retinal nerve fibers
- diplopia: secondary to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

Treatment

- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation as this increases likelihood of eventual development of MS

TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

Graves’ Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur secondary to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

Clinical

- initial inflammatory phase is followed by a quiescent cicatricial phase

Treatment

- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, ptosis and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides

Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjögren syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)
Giant Cell Arteritis/Temporal Arteritis

- see Rheumatology, R17

Clinical
- more common in women >60 yr
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and past medical history of polymyalgia rheumatica
- ischemic optic atrophy
  - 50% lose vision in other eye if untreated

Diagnosis
- temporal artery biopsy + increased ESR (ESR can be normal, but likely 80-100 in first hour, CRP
- if biopsy of one side is negative, biopsy the other side

Treatment
- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation (DO NOT WAIT TO TREAT)

Sarcoidosis

- granulomatous uveitis with large “mutton fat” keratic precipitates and posterior synechiae
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

Treatment
- steroids and mydriatics

Pediatric Ophthalmology

Strabismus

- ocular misalignment in one or both eyes, found in 3% of children
- object not visualized simultaneously by fovea of each eye
- terms used to describe strabismus depend upon
  - direction of deviation relative to the fixating eye
  - conditions under which it presents: ‘latent’, ‘manifest’ misalignment
  - change with the position of gaze: ‘comitant’ (usually nonparalytic), ‘incomitant’ (usually occurs with paralytic or restrictive strabismus)
- often presents with parental concern about a wandering eye, crossing eye, or poor vision
- elicit a detailed family history of strabismus, amblyopia, type of eyeglasses and history of wear, extraocular muscle surgery or other eye surgery, and genetic diseases to identify children at higher risk
- distinguish from pseudostrabismus (prominent epicanthal folds, hypertelorism, markedly positive or negative angle κ)
- complications: amblyopia, cosmesis

HETEROTROPIA
- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

Types
- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = “crossed-eyes”; exotropia = “wall-eyed”

Differentiate from Pseudostrabismus
- prominent epicanthal folds: give appearance of esotropia but Hirschberg test is normal, more common in Asians
- markedly elevated angle κ (the angle formed by the pupillary axis and the visual axis at the center of the pupil)
  - caused by the failure of optical axis of the eye and the visual axis to coincide
  - a small positive (up to 5°) angle κ is physiologic
  - a large positive angle κ (nasally deviated fovea) simulates eso-appearance
  - a large negative angle κ (temporally deviated fovea) gives an exo-appearance
Tests
- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - light reflex lateral to central cornea indicates esodeviation; light reflex medial to central cornea indicates exodeviation
  - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle $\kappa$)
- cover test
- the deviation can be quantified using prisms

HETEROPHORIA
- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- Hirschberg test will be normal (light reflexes symmetrical)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue)

Tests
- cover-uncover test
- alternate cover test
  - alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - maintain cover over one eye for 2-3 s before rapidly shifting to other eye

Table 9. Paralytic vs. Non-Paralytic Strabismus

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Paralytic Strabismus</th>
<th>Nonparalytic Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Incomitant strabismus</td>
<td>Concomitant strabismus</td>
</tr>
<tr>
<td>Onset</td>
<td>Often sudden but may be gradual or congenital</td>
<td>Usually gradual or shortly after birth; rarely sudden</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>Any age; most often acquired</td>
<td>Usually during infancy</td>
</tr>
<tr>
<td>Etiology</td>
<td>Reduction or restriction in range of eye movements due to:</td>
<td>Develops early in childhood</td>
</tr>
<tr>
<td></td>
<td>- Neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumor, trauma</td>
<td>No restriction in range of eye movements</td>
</tr>
<tr>
<td></td>
<td>- Muscular: myasthenia gravis (neuromuscular junction pathology), Graves’ disease</td>
<td>Monocular, alternating, or intermittent</td>
</tr>
<tr>
<td></td>
<td>- Structural: restriction or entrapment of extraocular muscles due to orbital</td>
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<tr>
<td></td>
<td>inflammation, tumor, fracture of the orbital wall</td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>Common</td>
<td>Uncommon; image from the misaligned eye is suppressed (see Amblyopia, OP40)</td>
</tr>
<tr>
<td>Visual Acuity in Other</td>
<td>Usually unaffected in the other eye, unless CN II is involved</td>
<td>Deviated eye may become amblyopic if not treated when the child is young</td>
</tr>
<tr>
<td>Eye</td>
<td></td>
<td>Amblyopia usually does not develop if child has alternating strabismus or intermittency, which allows neural pathways for both eyes to develop</td>
</tr>
<tr>
<td>Possibility of</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Amblyopia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic Findings or</td>
<td>May be present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Systemic Disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Accommodative Esotropia
- normal response to approaching object is the triad of the near reflex: convergence, accommodation and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 yr
- usually reversible with correction of refractive error

Non-accommodative Esotropia
- accounts for 50% of childhood strabismus
- most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

Amblyopia

Definition
- a neurodevelopmental visual disorder with unilateral (or less commonly, bilateral) reduction of best corrected visual acuity that cannot be attributed only and directly to the effect of a structural abnormality of the eye. It is caused by abnormal visual experience early in life and cannot be remedied immediately by spectacle glasses alone
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia). Other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors), and concomitant structural ocular problems

Detection
- "Holler Test": young child upset if good eye is covered
- quantitative visual acuity by age 3–4 yr using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
- prognosis: 90% will have good vision restored and maintained if treated <4 yr old

Etiology and Management
- strabismus
  - correct with glasses for accommodative esotropia (50% of children experience relief of their esotropia with glasses and will not require surgery)
  - occlusion of unaffected eye forces brain to use previously strabismic eye; aims to bring vision in previously suppressed eye to normal before surgery
  - surgery: recession (weakening) – moving muscle insertion further back on the globe; or resection (strengthening) – shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until approximately age 8 yr
- anisometropia
  - amblyopia usually in the more hyperopic eye
  - the more emmetropic (normal refraction) eye receives a clear image while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if visual acuity difference persists after 4-8 wk of using glasses
- deprivation amblyopia
  - occlusion due to ptosis, cataract, retinoblastoma, corneal opacity
  - occlusion amblyopia: prolonged patching of good eye may cause it to become amblyopic

Occlusion Therapy
- patching the good eye to force the brain to use the non-dominant eye and redevelop its vision
- atropine cycloplegic drops to impair accommodation and blur vision of the better seeing eye

Risks
- permanent loss of vision in the affected eye
- possibility of injury to ‘remaining’ good eye
  - safety glasses or polycarbonate lenses recommended if visual acuity in worse eye is <20/50
- loss of stereopsis
Essential Med Notes 2015 Pediatric Ophthalmology

Leukocoria

- white reflex (red reflex is absent)

Differential Diagnosis
- cataract
- retinoblastoma
- retinal coloboma
- ROP
- persistent hyperplastic primary vitreous
- Coat’s disease (exudative retinal telangiectasis)
- toxocariasis
- RD

Retinoblastoma

- most common primary intraocular malignancy in children
- incidence: 1/15,000; sporadic or genetic transmission; screening of siblings/offspring essential
- unilateral or bilateral (in 1/3 of cases)
- malignant – direct or hematogenous spread
- diagnosis
  - often presents with leukocoria or strabismus
  - U/S or CT scan may demonstrate calcified mass (present in most cases)

Treatment
- radiotherapy, chemotherapy combined with laser, cryopexy, and/or enucleation

Retinopathy of Prematurity

- vasoproliferative retinopathy that is a major cause of blindness in the developed world

Risk Factors
- non-black race (black infants have lower risk of developing ROP)
- low gestational age, birth weight <1500 g
- high oxygen exposure after birth

Classification (ROP Staging)
- stage 1: faint demarcation line at the junction between the vascularized and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial RD (4A: macula “on”, 4B: macula “off”)
- stage 5: total RD
- plus (+) disease: dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with 5 continuous or 8 cumulative clock hours of ROP involvement

Treatment
- threshold disease is treated with cryotherapy or laser (laser is now the standard treatment, with better refractive outcome), off label anti-VEGF intravitreal injections
- ROP beyond threshold level is either watched carefully (usually stage 4A) or treated with vitrectomy/scleral buckle

Prognosis
- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

Nasolacrimal System Defects

- congenital obstruction of the nasolacrimal duct (failure of canalization), usually occurs at 1–2 mo of age
- epiphora, crusting, discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac
- treatment: massage over lacrimal sac at medial corner of eyelid
- vast majority spontaneously resolve in 9–12 mo, otherwise consider referral for duct probing

Efficacy of Intravitreal Bevacizumab for Stage 3+ Retinopathy of Prematurity (ROP)

Study:
- Randomized controlled clinical trial.
- Patients: 150 infants born at gestational age ≤30 wk and birth weight ≤1500 g.
- Intervention: Randomized to conventional laser therapy or intravitreal bevacizumab monotherapy.
- Main Outcome: Recurrence of ROP in one or both eyes requiring retreatment before 54 wk postmenstrual age.
- Results: ROP recurrence was lower in the bevacizumab group (8 of 140 eyes [6%]) vs. the laser-therapy group (32 of 146 eyes [22%]) (p = 0.002). A significant treatment effect was found for zone I ROP (p = 0.003).
- Conclusions: Intravitreal bevacizumab monotherapy is beneficial for infants with zone I stage 3+ ROP and allows continued development of peripheral retinal vessels following treatment.

Zone I
- Zone II:
- Zone III:

Figure 27. Zones of the retina in ROP

Figure 28. Zones of the nasolacrimal system
**Ophthalmia Neonatorum**

- newborn conjunctivitis in first month of life
- causes
  - toxic: silver nitrate, erythromycin
  - infectious: bacterial (e.g. *N. gonorrhoeae* – most common, *C. trachomatis*), herpes simplex virus
- diagnose using stains and cultures
- treatment: systemic antibiotics with possible hospitalization if infectious etiology
- topical prophylaxis, most commonly with erythromycin (or silver nitrate), is required by law at birth

**Congenital Glaucoma**

- due to inadequate development of the filtering mechanism of the anterior chamber angle

**Clinical Features**

- cloudy cornea, increased IOP
- photophobia, epiphora
- buphthalmos (large cornea, “ox eye”, secondary to increased IOP), blepharospasm

**Treatment**

- filtration surgery is required soon after birth to prevent blindness

**Ocular Trauma**

**Blunt Trauma**

- caused by blunt object such as fist, squash ball
- history: injury, ocular history, drug allergy, tetanus status
- exam: VA first, pupil size and reaction, EOM (diplopia), external and slit-lamp exam, ophthalmoscopy
- if VA normal or slightly reduced, globe less likely to be perforated
- if VA reduced may be perforated globe, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion – detect with fluorescein staining and cobalt blue filter using slit-lamp or ophthalmoscope
- anterior chamber: assess depth, hyphema, hypopyon
- iris: prolapse, iritis
- lens: cataract, dislocation
- retinal tear/detachment

**Penetrating Trauma**

- include ruptured globe ± prolapsed iris, intraocular foreign body
- rule out intraocular foreign body, especially if history of “metal striking metal”, orbit CT
- **OCULAR EMERGENCY**: initial management - REFER IMMEDIATELY
  - ABCs
  - don’t press on eye globe!
  - don’t check IOP if possibility of globe rupture
  - check vision, diplopia
  - apply rigid eye shield to minimize further trauma
  - keep head elevated 30–45° to keep IOP down
  - keep NPO
  - tetanus status
  - give IV antibiotics
    - selecting appropriate agents depends on the mechanism of injury; gram positive bacteria are more commonly involved than gram negatives; retained intraocular foreign objects increase the risk of infections with Bacillus species, whereas exposure to vegetable matter increased the risk of a fungal etiology

**Post-Traumatic Infectious Endophthalmitis**

- **Surv Ophthalmol**: initial management - REFER IMMEDIATELY
  - **ABCs**
  - IV antibiotics
    - selecting appropriate agents depends on the mechanism of injury; gram positive bacteria are more commonly involved than gram negatives; retained intraocular foreign objects increase the risk of infections with Bacillus species, whereas exposure to vegetable matter increased the risk of a fungal etiology
Hyphema

- blood in anterior chamber often due to damage to root of the iris
- may occur with blunt trauma

**Treatment**
- refer to ophthalmology
  - shield and bedrest x 5 d or as determined by ophthalmologist
  - sleep with head upright
- may need surgical drainage if hyphema persists or if re-bleed

**Complications**
- risk of re-bleed highest on days 2-5, resulting in secondary glaucoma, corneal staining, and iris necrosis
- never prescribe Aspirin®, as it increases the risk of a re-bleed

Blow-Out Fracture

- see [Plastic Surgery, PL31](#)
- blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
- orbital rim remains intact
- inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
- infraorbital nerve courses along the floor of the orbit and may be damaged

**Clinical Features**
- pain and nausea at time of injury
- diplopia, restriction of EOM
- infraorbital and upper lip paresthesia (CN V2)
- enophthalmos (sunken eye), periorbital ecchymoses

**Investigations**
- plain films: Waters' view and lateral
- CT: anteroposterior and coronal view of orbits

**Treatment**
- refrain from coughing, blowing nose
- systemic antibiotics may be indicated
- surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
- may delay surgery if the diplopia improves

Chemical Burns

- alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
- poor prognosis if cornea opaque, likely irreversible stromal damage
- even with a clear cornea initially, alkali burns can progress for weeks (thus, very guarded prognosis)

**Treatment**
- immediately irrigate at site of accident with water or buffered solution
  - IV drip for at least 20-30 min with eyelids retracted in emergency department
  - swab upper and lower fornices to remove possible particulate matter
- do not attempt to neutralize because the heat produced by the reaction will damage the cornea
- cycloplegic drops to decrease iris spasm (pain) and prevent secondary glaucoma (due to posterior synechiae formation)
- topical antibiotics and patching
- topical steroids (by ophthalmologist) to decrease inflammation, use for <2 wk (in the case of a persistent epithelial defect)
Surgical Ophthalmology

- dacrocystorhinostomy (DCR): excision of bone covering the nasolacrimal sac to restore tear drainage
- LASIK (laser-assisted *in situ* keratomileusis): a microkeratome is used to create a corneal flap followed by laser remodeling of the stroma to correct refractive error
- trabeculectomy: creation of a new outflow tract from anterior chamber to under conjunctiva; fibrosis prevented with mitomycin C or 5-FU injection during surgery
- phacoemulsification (cataract extraction): the use of ultrasonic waves to break up and aspirate a cataract followed by replacement with an artificial lens implant
- femtosecond laser-assisted cataract surgery: uses focused ultrashort pulses (10^-15 of a second) to perform photodissection in achieving capsulorrhexis and lens fragmentation
- vitrectomy: the use of small gauge trochars to enter the posterior segment and remove vitreous; commonly used to treat vitreous hemorrhage and RD
- pneumatic retinopexy: intraocular injection of air or an expandable gas in order to tamponade a retinal break for repair of RD
- scleral buckle: a silicone band is secured on the outside of the globe that indents the eye wall, thereby relieving vitreous traction on the retina around any tears/holes and allowing the tears/holes to remain sealed for repair of RD
- minimally invasive glaucoma surgery (MIGS): implantation of IOP lowering drainage devices (e.g. iStent) through an ab interno microincisional approach during cataract surgery

Ocular Drug Toxicity

Table 10. Drugs with Ocular Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Corneal microdeposits and superficial keratopathy (vortex keratopathy) Rare: ischemic optic neuropathy</td>
</tr>
<tr>
<td>Atropine, benztropine</td>
<td>Pupillary dilation (risk of angle closure glaucoma)</td>
</tr>
<tr>
<td>Bisphosphonates (Fosamax®, Actonel®)</td>
<td>Inflammatory eye disease (iritis, scleritis, episcleritis)</td>
</tr>
<tr>
<td>Chloroquine, hydroxychloroquine</td>
<td>Bull’s eye maculopathy Vortex keratopathy</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Anterior subcapsular cataract</td>
</tr>
<tr>
<td>Contraceptive pills</td>
<td>Decreased tolerance to contact lenses Migraine Optic neuritis Central vein occlusion, benign increase intracranial pressure</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Yellow vision Blurred vision</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Foscarnet (Haldol®)</td>
<td>Oculogyric crises Blurred vision</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Superficial keratopathy</td>
</tr>
<tr>
<td>Interferon</td>
<td>Retinal hemorrhages and cotton wool spots</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Steroids</td>
<td>Posterior subcapsular cataracts Glaucoma Papilledema (systemic steroids) Increased severity of HSV infections (geographic ulcers) Predisposition to fungal infections</td>
</tr>
<tr>
<td>Sulphonamides, NSAIDs</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Tamsulosin (Flomax®)</td>
<td>Intraoperative Floppy Iris Syndrome, which can complicate cataract surgery</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Papilledema (associated with pseudotumor cerebri)</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Pigmentary degeneration of retina</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Retinal deposition with macular sparing, peripheral visual field loss</td>
</tr>
<tr>
<td>Vitamin A toxicity</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Vitamin D toxicity</td>
<td>Band keratopathy</td>
</tr>
</tbody>
</table>

Common Medications

TOPICAL OCULAR DIAGNOSTIC DRUGS

Fluorescein Dye
- water soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope or slit-lamp)
- absorbed in areas of epithelial loss (ulcer or abrasion)
- also stains mucus and contact lenses
Rose Bengal Stain
• stains devitalized epithelial cells and mucus

Anesthetics
• e.g. proparacaine HCl 0.5%, tetracaine 0.5%
• indications: removal of foreign body and sutures, tonometry, examination of painful cornea
• toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore NEVER prescribe

Mydriatics
• dilate pupils
• two classes
  ▪ cholinergic blocking (e.g. tropicamide – Mydriacyl®)
    ▪ dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    ▪ indications: refraction, ophthalmoscopy, therapy for iritis
  ▪ adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    ▪ stimulate pupilary dilator muscles, no effect on accommodation
    ▪ usually used with tropicamide for additive effects
    ▪ side effects: HTN, tachycardia, arrhythmias

Table 11. Mydriatic Cycloplegic Drugs and Duration of Action

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide (Mydriacyl®) 0.5%, 1%</td>
<td>4-5 h</td>
</tr>
<tr>
<td>Cyclopentolate HCl 0.5%, 1%</td>
<td>3-6 h</td>
</tr>
<tr>
<td>Homatropine HBr 1%, 2%</td>
<td>3-7 d</td>
</tr>
<tr>
<td>Atropine sulfate 0.5%, 1%</td>
<td>1-2 wk</td>
</tr>
<tr>
<td>Scopolamine HBr 0.25%, 5%</td>
<td>1-2 wk</td>
</tr>
</tbody>
</table>

GLAUCOMA MEDICATIONS

Table 12. Glaucoma Medications

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Dose</th>
<th>Effect</th>
<th>Comment/Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Agonist</td>
<td></td>
<td>1 gtt OS/OD bid/tid</td>
<td></td>
</tr>
<tr>
<td>epinephrine HCl 1% (Epin®)</td>
<td></td>
<td>2. Selective: ↓ aqueous production + ↑ uveoscleral outflow</td>
<td>2. Selective: contact allergy, hypotension in children</td>
</tr>
<tr>
<td>dipivalyl epinephrine 0.1% (Propine®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α₂-selective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>brimonidine 0.2% (Alphagan®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>apraclonidine 0.5% (luptane®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td></td>
<td>1 gtt OS/OD qd/bid</td>
<td>Bronchospasm (caution in asthma/COPD)</td>
</tr>
<tr>
<td>Non-selective</td>
<td></td>
<td>*)</td>
<td>↑ CHF, Bradycardia</td>
</tr>
<tr>
<td>timolol (Timoptic®)</td>
<td></td>
<td></td>
<td>Hypotension, Depression, Heart block, Impotence</td>
</tr>
<tr>
<td>levobunolol (Betagan®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β₁-selective</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>betaxolol (Betoptic®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbonic Anhydrase Inhibitor</td>
<td></td>
<td>1 gtt OS/OD tid Diamox®, 500 mg PO bid</td>
<td>Must ask about sulfa allergy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*)</td>
<td>Generally local side effects with topical preparations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Oral: diarrhoea, fatigue, paresthesias, GI upset, etc.</td>
</tr>
<tr>
<td>Parasympathomimetic (cholinergic stimulating)</td>
<td></td>
<td>1-2 gtt OS/OD tid/pid</td>
<td>Miosis, ↓ right vision, ↑ GI motility, Brow ache, Headache, ↓ heart rate</td>
</tr>
<tr>
<td>pilocarpine (Pilopine®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>carbachol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostaglandin Analogues</td>
<td></td>
<td>1 gtt OS/OD qhs</td>
<td>Iris color change, Periorbital skin pigmentation, Lash growth, Conjunctival hyperemia</td>
</tr>
<tr>
<td>latanoprost (Kalatan®)</td>
<td></td>
<td>↑ uveoscleral outflow (uveoscleral responsible for 20% of drainage)</td>
<td></td>
</tr>
<tr>
<td>bimatoprost (Lumigan®)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

VEGF Inhibitors
• block VEGF which prevents ocular angiogenesis and further development of choroidal neovascularization
• administered via intravitreal injections
• pegaptanib (Macugen®) is a selective anti-VEGF targeting VEGF isoform 165 (no longer widely used)
TOPICAL OCULAR THERAPEUTIC DRUGS

NSAIDs
- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

Antihistamines
- used to relieve red and itchy eye, often in combination with decongestants
- sodium cromoglicate - stabilizes membranes

Decongestants
- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine
- rebound vasodilation with overuse; rarely can precipitate angle closure glaucoma

Antibiotics
- indications: bacterial conjunctivitis, keratitis, or blepharitis
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (ciprofloxacin [Ciloxan®], ofloxacin [Ocuflox®], moxifloxacin [Vigamox®], gatifloxacin [Zymar®])

Corticosteroids
- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Pred Forte® 1%), rimexolone (Voxol®), loteprednol etabonate 0.5% (Lotamax®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  - potentiates HSV keratitis and fungal keratitis as well as masks symptoms
  - increased IOP, more rapidly in steroid responders (within weeks)
  - posterior subcapsular cataract (within months)

References

ACCORD Study Group; ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes NEJM 2010;363:233-244


Shmerling RH, Smetana GW. Does this patient have temporal arteritis? JAMA 2010;303:1265-71.


Basic Anatomy Review

Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles
Figure 2. (Left) Blood supply to the upper limb (Right) Axillary and radial nerves: innervation of the upper limb.

Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Motor</th>
<th>Sensory</th>
<th>Nerve Roots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary</td>
<td>Deltoid/Teres Minor</td>
<td>Lateral Upper Arm (Sergeant’s Patch)</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>Biceps/Brachials</td>
<td>Lateral Forearm</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Radial</td>
<td>Triceps</td>
<td>Lateral Dorsum of the Hand</td>
<td>C5, C6, C7, C8</td>
</tr>
<tr>
<td></td>
<td>Wrist/Thumb/Finger Extensors</td>
<td>Medial Upper Forearm</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>Wrist Flexors and Adductors</td>
<td>Volar Thumb to Radial half of 4th Digit</td>
<td>C6, C7</td>
</tr>
<tr>
<td></td>
<td>Flexion of the 1st-3rd Digits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulnar</td>
<td>Wrist Flexors and Adductors</td>
<td>Medial Forearm and Volar of Hand</td>
<td>C8, T1</td>
</tr>
<tr>
<td></td>
<td>Flexion of the 4th-5th Digits</td>
<td>(Ulnar half of 4th and 5th Digit)</td>
<td></td>
</tr>
<tr>
<td>Tibial</td>
<td>Ankle Plantar Flexion</td>
<td>Sole of Foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td></td>
<td>Knee Flexion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Great Toe Flexion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial Peroneal</td>
<td>Ankle Eversion</td>
<td>Dorum of Foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Deep Peroneal</td>
<td>Ankle Dorsiflexion and Inversion</td>
<td>1st Web Space</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Sural</td>
<td></td>
<td>Lateral Foot</td>
<td>S1, S2</td>
</tr>
<tr>
<td>Saphenous</td>
<td></td>
<td>Anteromedial Ankle</td>
<td>L3, L4</td>
</tr>
</tbody>
</table>
Figure 3. Nerves and arteries of lower limbs

Differential Diagnosis of Joint Pain

Extrinsic

- Generalized
  - Fibromyalgia, dermatomyositis
- Neurologic
  - Nerve root compression, HZV
- Generalized
  - Fibromyalgia, dermatomyositis
- Referred Pain
  - From nearby organs or tissue

Intrinsic

- Articular
  - Arthritis, neoplasm, trauma
- Non-articular
  - Bursitis, tendinitis, myositis

Figure 4. Intrinsic vs. extrinsic joint pain
Fractures – General Principles

Fracture Description

1. Integrity of Skin/Soft Tissue
   - closed: skin/soft tissue over and near fracture is intact
   - open: skin/soft tissue over and near fracture is lacerated or abraded, fracture exposed to outside environment
     - signs: continuous bleeding from puncture site or fat droplets in blood are suggestive of an open fracture

2. Location
   - epiphyseal: end of bone, forming part of the adjacent joint
   - metaphyseal: the flared portion of the bone at the ends of the shaft
   - diaphyseal: the shaft of a long bone (proximal, middle, distal)
   - physis: growth plate

3. Orientation/Fracture Pattern
   - transverse: fracture line perpendicular to long axis of bone; result of direct high energy force
   - oblique: angular fracture line; result of angular or rotational force
   - butterfly: fracture site fragment which looks like a butterfly
   - segmental: a separate segment of bone bordered by fracture lines; result of high energy force
   - spiral: complex, multi-planar fracture line; result of rotational force, low energy
   - comminuted/multi-fragmentary: >2 fracture fragments
   - intra-articular: fracture line crosses articular cartilage and enters joint
   - avulsion: tendon or ligament tears/pulls off bone fragment; often in children, high energy
   - compression/impacted: impaction of bone; typical sites are vertebrae or proximal tibia
   - torus: a buckle fracture of one cortex, often in children (see Figure 51, OR39)
   - greenstick: an incomplete fracture of one cortex, often in children (see Figure 51, OR39)
   - pathologic: fracture through bone weakened by disease/tumor

4. Displacement
   - nondisplaced: fracture fragments are in anatomic alignment
   - displaced: fracture fragments are not in anatomic alignment
   - distracted: fracture fragments are separated by a gap (opposite of impacted)
   - impacted: fracture fragments are compressed, resulting in shortened bone
   - angulated: direction of fracture apex, e.g. varus/valgus
   - translated/shifted: percentage of overlapping bone at fracture site
   - rotated: fracture fragment rotated about long axis of bone

Management of Fractures

- ABCs, primary survey and secondary survey (ATLS protocol)
  - rule out other fractures/injuries
  - rule out open fracture (see sidebar, OR6)
- AMPLE history: Allergies, Medications, Past medical history, Last meal, Events surrounding injury
  - consider pathologic fracture with history of only minor trauma
- analgesia
- imaging
- splint extremity

Figure 6. Fracture types

Figure 5. Schematic diagram of the long bone

X-Ray Rule of 2s
2 sides = bilateral
2 views = AP + lateral
2 joints = joint above + below
2 times = before + after reduction

Varus/Valgus Angulation
Varus = Apex away from midline
Valgus = Apex toward midline

Displacement
Refers to position of the distal fragment relative to the proximal fragment

Quick Nerve Exam
“Thumbs Up”: PIN (Radial Nerve)
“OK Sign”: AIN (Median Nerve)
“Spread Fingers”: Ulnar Nerve

Reasons for Splinting
- Pain control
- Reduces further damage to vessels, nerves, and skin
- Decreases risk of inadvertently converting closed to open fracture
- Facilitates patient transport
1. obtain the reduction (for appropriate IV sedation see Table 28, OR47)
   - closed reduction
     - apply traction in the long axis of the limb
     - reverse the mechanism that produced the fracture
     - reduce with IV sedation and muscle relaxation (fluoroscopy can be used if available)
   - indications for open reduction
     - “NO CAST”
     - other indications include
       - failed closed reduction
       - not able to cast or apply traction due to site (e.g. hip fracture)
       - pathologic fractures
       - potential for improved function with ORIF
   - ALWAYS re-check NVS after reduction and obtain post-reduction x-ray
2. maintain the reduction
   - external stabilization: splints, casts, traction, external fixator
   - internal stabilization: percutaneous pinning, extramedullary fixation (screws, plates, wires), IM fixation (rods)
   - follow-up: evaluate bone healing
3. rehabilitate to regain function and avoid joint stiffness

**Fracture Healing**

**Normal Healing**

- Weeks 0-3: Hematoma, macrophages surround fracture site
- Weeks 3-6: Osteoclasts remove sharp edges, callus forms within hematoma
- Weeks 6-12: Bone forms within the callus, bridging fragments
- Months 6-12: Cortical gap is bridged by bone
- Years 1-2: Normal architecture is achieved through remodelling

**Evaluation of Healing: Tests of Union**

- clinical: no longer tender to palpation or stressing on physical exam
- x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

**General Fracture Complications**

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compartment syndrome</td>
<td>Mal-/non-union</td>
</tr>
<tr>
<td>Neurological injury</td>
<td>AVN</td>
</tr>
<tr>
<td>Vascular injury</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Infection</td>
<td>HD</td>
</tr>
<tr>
<td>Implant failure</td>
<td>Post-traumatic OA</td>
</tr>
<tr>
<td>Fracture blisters</td>
<td>Joint stiffness/adhesive capsulitis</td>
</tr>
<tr>
<td></td>
<td>CRPS type I/ RSD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td></td>
</tr>
<tr>
<td>ARDS secondary to fat embolism</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic shock</td>
<td></td>
</tr>
</tbody>
</table>

**Articular Cartilage**

**Properties**

- 2-4 mm layer covering ends of articulating bones, provides nearly frictionless surface
- avascular (nutrition from synovial fluid), aneural, alymphatic
- composed of: collagen (90% is type II; gives tensile strength), water, proteoglycans (gives compressive strength), and chondrocytes
ARTICULAR CARTILAGE DEFECTS

Etiology
• overt trauma, repetitive minor trauma (such as patellar maltracking); common sports injury
• degenerative conditions such as early stage OA or osteochondritis dissecans

Clinical Features
• similar to symptoms of OA (joint line pain with possible effusion, etc.)
• often have predisposing factors, such as ligament injury, malalignment of the joint (varus/valgus), obesity, bone deficiency (AVN, osteochondritis dissecans, ganglion bone cysts), inflammatory arthropathy, and familial osteoarthropathy
• may have symptoms of locking or catching related to the torn/displaced cartilage

Investigations
• x-ray (to rule out bony defects and check alignment)
• MRI
• diagnostic arthroscopy (treatment is often guided by what is seen during arthroscopy)

Table 3. Outerbridge Classification of Chondral Defects

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chondral Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Softening and swelling of cartilage</td>
</tr>
<tr>
<td>II</td>
<td>Fragmentation and fissuring &lt;1/2” in diameter</td>
</tr>
<tr>
<td>III</td>
<td>Fragmentation and fissuring &gt;1/2” in diameter</td>
</tr>
<tr>
<td>IV</td>
<td>Erosion of cartilage down to bone</td>
</tr>
</tbody>
</table>

Treatment
• individualized; must take into account patient factors (age, skeletal maturity, activity level, etc.) and defect factors (Outerbridge classification, subchondral bone involvement, etc.)
• non-operative: rest, NSAIDs, bracing
• operative: microfracture, osteochondral grafting (autograft or allograft), autologous chondrocyte implantation

Orthopedic X-Ray Imaging

General Principles
• x-ray 1 joint above and 1 below
• obtain at least 2 orthogonal views ± specialized views

Table 4. Orthopedic X-Ray Imaging

<table>
<thead>
<tr>
<th>Site</th>
<th>Injury</th>
<th>X-Ray Views</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>Anterior dislocation</td>
<td>AP, Axillary ± stress view with 10 lb in hand, Zanca view (10-15 cephalic tilt)</td>
</tr>
<tr>
<td></td>
<td>Posterior dislocation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>AC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frozen shoulder</td>
<td></td>
</tr>
<tr>
<td>Arm</td>
<td>Humerus #</td>
<td>AP, Lateral, Trans-scapular, Axillary</td>
</tr>
<tr>
<td>Elbow/Forearm</td>
<td>Supracondylar #</td>
<td>AP, Lateral</td>
</tr>
<tr>
<td></td>
<td>Radial head #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monteggia #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Night stick #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galeazzi #</td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>Colles #</td>
<td>AP, Lateral</td>
</tr>
<tr>
<td></td>
<td>Smith #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scaphoid #</td>
<td>Scaphoid (wrist extension and ulnar deviation x 2 wk)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Pelvic #</td>
<td>AP, Pelvis, Inlet and outlet views, Judet views (obturator and iliac oblique for acetabular #)</td>
</tr>
<tr>
<td>Hip</td>
<td>Femoral head/neck #</td>
<td>AP, Lateral, Frog-leg lateral, Dunn</td>
</tr>
<tr>
<td></td>
<td>Intertrochanteric #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCFE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FAI</td>
<td></td>
</tr>
</tbody>
</table>
Orthopedic Emergencies

Trauma Patient Workup

Etiology
- high energy trauma, e.g. MVC, fall from height
- may be associated with spinal injuries or life-threatening visceral injuries

Clinical Presentation
- local swelling, tenderness, deformity of the limbs, and instability of the pelvis or spine
- decreased level of consciousness, hypotension/hypovolemia
- consider involvement of EtOH or other substances

Investigations
- trauma survey (see Emergency Medicine, ER5)
- x-rays: lateral cervical spine, AP chest, AP pelvis, AP and lateral of all bones suspected to be injured
- other views of pelvis: AP, inlet, and outlet; Judet views for acetabular fracture (for classification of pelvic fractures see Table 19, OR26)

Treatment
- ABCDEs and initiate resuscitation for life threatening injuries
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- DVT prophylaxis

Complications
- hemorrhage – life threatening (may produce signs and symptoms of hypovolemic shock)
- fat embolism syndrome (SOB, hypoxemia, petechial rash, thrombocytopenia, and neurological symptoms)
- venous thrombosis – DVT and PE
- bladder/urethral/bowel injury
- neurological damage
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic OA of joints with intra-articular fractures
- sepsis if missed open fracture

Open Fractures

Definition
- fractured bone and hematoma in communication with the external environment

Emergency Measures
- removal of obvious foreign material
- irrigate with normal saline if grossly contaminated

Table 4. Orthopedic X-Ray Imaging (continued)

<table>
<thead>
<tr>
<th>Site</th>
<th>Injury</th>
<th>X-Ray Views</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>Knee dislocation</td>
<td>AP standing, lateral</td>
</tr>
<tr>
<td></td>
<td>Femur/tibia #</td>
<td>Skyline – tangential view with knees flexed at 45° to see patellofemoral joint</td>
</tr>
<tr>
<td></td>
<td>Patella #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patella dislocation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patella femoral syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tibia shaft #</td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>Ankle #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortise view: ankle at 15° of internal rotation</td>
</tr>
<tr>
<td>Foot</td>
<td>Talar #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Calcaneal #</td>
<td>Lateral</td>
</tr>
<tr>
<td>Spine</td>
<td>Compression #</td>
<td>AP spine</td>
</tr>
<tr>
<td></td>
<td>Burst #</td>
<td>AP odontoid</td>
</tr>
<tr>
<td></td>
<td>Cervical spine #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oblique</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swimmer’s view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral flexion/extension view: evaluate subluxation of cervical vertebra</td>
</tr>
</tbody>
</table>

Buck’s Traction
A system of weights, pulleys, and ropes that are attached to the end of a patient’s bed exerting a longitudinal force on the distal end of a fracture, improving its length, alignment, and rotation

Orthopedic Emergencies

VON CHOP
Vascular compromise
Open fracture
Neurological compromise/cauda equina syndrome
Compartment syndrome
Hip dislocation
Osteomyelitis/septic arthritis
Unstable Pelvic fracture

Antibiotics for Preventing Infection in Open Limb Fractures
Cochrane DB Syst Rev 2004;1:CD003764
Purpose: To review the evidence regarding the effectiveness of antibiotics in the initial treatment of open fractures of the limbs.
Methods: Randomized or quasi randomized controlled trials comparing antibiotic treatment with placebo or no treatment in preventing acute wound infection were identified and reviewed. Data were extracted and pooled for analysis.
Results: Eight studies (n=1,106) were reviewed. The use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo (RRR=0.43, 95% CI 0.29, 0.65; ARR=0.07, 95% CI 0.03=0.10).
Conclusions: Antibiotics reduce the incidence of early infections in open fractures of the limbs.

33% of patients with open fractures have multiple injuries
• cover wound with sterile dressings
• immediate IV antibiotics
• tetanus toxoid or immunoglobulin as needed
• reduce and splint fracture
• NPO and prepare for OR (blood work, consent, ECG, CXR)
  • traumatic wound often left open to drain but vacuum-assisted closure dressing may be used
  • re-examine with repeat I&D in 48 h

Table 5. Gustilo Classification of Open Fractures

<table>
<thead>
<tr>
<th>Gustilo Grade</th>
<th>Length of Open Wound</th>
<th>Description</th>
<th>Prophylactic Antibiotic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;1 cm</td>
<td>Minimal contamination and soft tissue injury Simple or minimally comminuted fracture</td>
<td>First generation cephalosporin (cefazolin) for 3 d If allergy use fluoroquinolone If MRSA positive use vancomycin</td>
</tr>
<tr>
<td>II</td>
<td>1-10 cm</td>
<td>Moderate contamination Soft tissue injury</td>
<td>First generation cephalosporin (cefazolin) for 3 d plus Gram-negative coverage (gentamicin) for at least 3 d</td>
</tr>
<tr>
<td>III*</td>
<td>&gt;10 cm</td>
<td>IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound IIIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound IIIC: Vascular injury/compromise</td>
<td>As per Grade II For soil contamination, penicillin is added for clostridial coverage</td>
</tr>
</tbody>
</table>

*Any high energy, comminuted fracture, shot gun, farmyard/water contamination, exposure to oral flora, or fracture >8 h old is immediately classified as Grade III

Cauda Equina Syndrome
• see Neurosurgery, NS26

Compartment Syndrome

Definition
• increased interstitial pressure in an anatomical compartment (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment) with little room for expansion
• interstitial pressure exceeds capillary perfusion pressure leading to muscle necrosis (in 4-6 h) and eventually nerve necrosis

Etiology
• intracompartmental: fracture (particularly tibial shaft fractures, pediatric supracondylar fractures, and forearm fractures), crush injury, ischemia-reperfusion injury
• extracompartmental: constrictive dressing (circumferential cast, poor positioning during surgery), circumferential burn

Figure 9. Pathogenesis of compartment syndrome

Clinical Features
• pain with active contraction of compartment
• pain with passive stretch
• swollen, tense compartment
• suspicious history

• 5 Ps: late sign – do not wait for these to develop to make the diagnosis!
Investigations
- usually not necessary as compartment syndrome is a clinical diagnosis
- in children or unconscious patients where clinical exam is unreliable, compartment pressure
  monitoring with catheter AFTER clinical diagnosis is made (normal = 0 mmHg; elevated
  ≥30 mmHg or ≤30 mmHg of diastolic BP)

Treatment
- non-operative
  - remove constrictive dressings (casts, splints), elevate limb at the level of the heart
- operative
  - urgent fasciotomy
    - 48-72 h post-operative: wound closure ± necrotic tissue debridement

Complications
- rhabdomyolysis, renal failure secondary to myoglobinuria
- Volkmann’s ischemic contracture: ischemic necrosis of muscle, followed by secondary fibrosis
  and finally calcification; especially following supracondylar fracture of humerus

Osteomyelitis

Etiology
- most commonly caused by *Staphylococcus aureus*
- mechanism of spread: hematogenous (most common) vs. direct-inoculation vs. contiguous focus
- risk factors: recent trauma/surgery, immunocompromised patients, DM, IV drug use, poor vascular supply, peripheral neuropathy

Clinical Presentation
- symptoms: pain and fever
- on exam: erythema, tenderness, edema common ± abscess/draining sinus tract; impaired function/WB

Diagnosis
- see Medical Imaging, MI24
- workup includes: WBC and diff, ESR, CRP, blood culture, aspirate culture/bone biopsy

Table 6. Treatment of Osteomyelitis

<table>
<thead>
<tr>
<th>Acute Osteomyelitis</th>
<th>Chronic Osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV antibiotics 4-6 wk; started empirically and adjusted after obtaining blood and aspirate cultures ± surgery (I&amp;D) for abscess or significant involvement ± hardware removal (if present)</td>
<td>Surgical debridement Antibiotics: both local (e.g. antibiotic beads) and systemic (IV)</td>
</tr>
</tbody>
</table>

Septic Joint

Etiology
- most commonly caused by *Staphylococcus aureus* in adults
- consider coagulase-negative *Staphylococcus* in patients with prior joint replacement
- consider *Neisseria gonorrhoeae* in sexually active adults and newborns
- risk factors: age >80 yr, DM, RA, prosthetic joint, recent joint surgery, skin infection/ulcer, IV drug use, alcoholism, previous intra-articular corticosteroid injection

Clinical Presentation
- inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling, pain on active and passive ROM, ± fever

Investigations
- x-ray (to rule out fracture, tumor, metabolic bone disease), ESR, CRP, WBC, blood cultures
- joint aspirate: WBC >80,000 with >90% neutrophils, protein level >4.4 mg/dL, joint glucose level < blood glucose level, no crystals, positive Gram stain results
- listen for heart murmur (to reduce suspicion of infective endocarditis, use Duke Criteria)

Treatment
- IV antibiotics, empiric therapy (based on age and risk factors), adjust following joint aspirate C&S results
- for small joints: needle aspiration, serial if necessary until sterile
- for major joints such as knee, hip, or shoulder: urgent decompression and surgical drainage

Plain Film Findings of Osteomyelitis
- Soft tissue swelling
- Lytic bone destruction*
- Periosteal reaction (formation of new bone, especially in response to #)*
  - *Generally not seen on plain films until 10-12 d after onset of infection

Plain Film Findings in a Septic Joint
- Early (0-3 d): usually normal; may show soft-tissue swelling or joint space widening from localized edema
- Late (4-6 d): joint space narrowing and destruction of cartilage

Serial C-reactive protein (CRP) can be used to monitor response to therapy
Shoulder Dislocation

Prognosis
- recurrence rate depends on age of first dislocation: <20 yr = 65-95%; 20-40 yr = 60-70%; >40 yr = 2-4%

Specific Complications
- rotator cuff or capsular tear, shoulder stiffness
- injury to axillary nerve/artery, brachial plexus
- recurrent/unreduced dislocation (most common complication)

Investigations
- anterior dislocation x-rays (AP, trans-scapular, axillary views)
- posterior dislocation x-rays (AP, trans-scapular, axillary) or CT scan

Table 7. Anterior and Posterior Shoulder Dislocation

<table>
<thead>
<tr>
<th>Anterior Shoulder Dislocation (&gt;90%)</th>
<th>Posterior Shoulder Dislocation (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td></td>
</tr>
<tr>
<td>Abducted arm is externally rotated/hyperextended, or blow to posterior shoulder</td>
<td>Adducted, internally rotated, flexed arm</td>
</tr>
<tr>
<td>Involuntary, usually traumatic; voluntary, atraumatic</td>
<td>3 Es (epileptic seizure, EtOH, electrocution)</td>
</tr>
<tr>
<td>Foodsh</td>
<td>Blow to anterior shoulder</td>
</tr>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Pain, arm slightly abducted and externally rotated with inability to internally rotate</td>
<td>Pain, arm is held in adduction and internal rotation; external rotation is blocked</td>
</tr>
<tr>
<td><strong>Shoulder Exam</strong></td>
<td></td>
</tr>
<tr>
<td>“Squared off” shoulder</td>
<td>Anterior shoulder flattening, prominent coracoid, palpable mass posterior to shoulder</td>
</tr>
<tr>
<td>Positive apprehension test: patient looks apprehensive with gentle shoulder abduction and external rotation to 90° since humeral head is pushed anteriorly and recreates feeling of anterior dislocation (see Figure 13)</td>
<td>Positive posterior apprehension (“jerk”) test: with patient supine, flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will “jerk” back with the sensation of subluxation (see Figure 13)</td>
</tr>
<tr>
<td>Positive relocation test: a posteriorly directed force applied during the apprehension test relieves apprehension since anterior subluxation is prevented</td>
<td>Note: the posterior apprehension test is used to test for recurrent posterior instability, NOT for acute injury</td>
</tr>
<tr>
<td>Positive sulcus sign: presence of subacromial indentation with distal traction on humerus indicates inferior shoulder instability (see Figure 13)</td>
<td></td>
</tr>
<tr>
<td><strong>Neurovascular Exam Including</strong></td>
<td></td>
</tr>
<tr>
<td>Axillary nerve: sensory patch over deltoid and deltoid contraction</td>
<td>Full neurovascular exam as per anterior shoulder dislocation</td>
</tr>
<tr>
<td>Musculocutaneous nerve: sensory patch on lateral forearm and biceps contraction</td>
<td></td>
</tr>
<tr>
<td><strong>RADIOGRAPHIC FINDINGS</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Axillary View</strong></td>
<td>Humeral head is anterior</td>
</tr>
<tr>
<td>Humeral head is anterior to the center of the “Mercedes-Benz” sign</td>
<td>Humeral head is posterior to center of “Mercedes-Benz” sign</td>
</tr>
<tr>
<td><strong>Trans-scapular ‘Y’ View</strong></td>
<td>Humeral head is posterior</td>
</tr>
<tr>
<td>Partial vacancy of glenoid fossa (vacant glenoid sign) and &gt;6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign)</td>
<td></td>
</tr>
<tr>
<td><strong>AP View</strong></td>
<td>Humeral head is posterior</td>
</tr>
<tr>
<td>Sub-coracoid lie of the humeral head is most common</td>
<td>Humeral head is posterior</td>
</tr>
<tr>
<td><strong>Hill-Sachs and Bony Bankart Lesions</strong></td>
<td>Humeral head is posterior</td>
</tr>
<tr>
<td>± Hill-Sachs lesion: compression fracture of posterior humeral head due to forceful impaction of an anteriorly dislocated humeral head against the glenoid rim (see Figure 12)</td>
<td>± reverse Hill-Sachs lesion (75% of cases): divot in anterior humeral head</td>
</tr>
<tr>
<td>± bony Bankart lesion: avulsion of the anterior glenoid labrum (with attached bone fragments) from the glenoid rim (see Figure 12)</td>
<td>± reverse bony Bankart lesion: avulsion of the posterior glenoid labrum from the bony glenoid rim</td>
</tr>
</tbody>
</table>

Factors Causing Shoulder Instability
- Shallow glenoid
- Loose capsule
- Ligamentous laxity

Frequency of Dislocations:
- Anterior shoulder > Posterior shoulder

The glenohumeral joint is the most commonly dislocated joint in the body since stability is sacrificed for motion.

Figure 10. Shoulder joints

There are 4 Joints in the Shoulder: glenohumeral, AC, sternoclavicular (SC), scapulothoracic


Figure 11. Mercedes-Benz

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Coracoid process
Acromion
Humerus
Scapula
Table 7. Anterior and Posterior Shoulder Dislocation (continued)

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Anterior Shoulder Dislocation (&gt;90%)</th>
<th>Posterior Shoulder Dislocation (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed reduction with IV sedation and muscle relaxation</td>
<td>Closed reduction with sedation and muscle relaxation</td>
<td></td>
</tr>
<tr>
<td>Traction-countertraction: assistant stabilizes torso with a folded sheet wrapped across the chest while the surgeon applies gentle steady traction</td>
<td>Inferior traction on a flexed elbow with pressure on the back of the humeral head</td>
<td></td>
</tr>
<tr>
<td>Stimson: while patient lies prone with arm hanging over table edge, hang a 5 lb weight on wrist for 15-20 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocratic method: place heel into patient’s axilla and apply traction to arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunningham’s method: low risk, low pain; if not successful try above methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtain post-reduction x-rays</td>
<td>Obtain post-reduction x-rays</td>
<td></td>
</tr>
<tr>
<td>Check post-reduction NVS</td>
<td>Check post-reduction NVS</td>
<td></td>
</tr>
<tr>
<td>Sling x 3 wk (avoid abduction and external rotation), followed by shoulder rehabilitation (dynamic stabilizer strengthening)</td>
<td>Sling in abduction and external rotation x 3 wk, followed by shoulder rehabilitation (dynamic stabilizer strengthening)</td>
<td></td>
</tr>
</tbody>
</table>

Rotator Cuff Disease

- rotator cuff consists of 4 muscles that act to stabilize humeral head within the glenoid fossa

Table 8. Rotator Cuff Muscles

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Muscle Attachments</th>
<th>Nerve Supply</th>
<th>Muscle Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>Distal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraspinatus</td>
<td>Scapula; greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
<td>Abduction</td>
</tr>
<tr>
<td>Infraspinatus</td>
<td>Scapula; greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
<td>External rotation</td>
</tr>
<tr>
<td>Teres Minor</td>
<td>Scapula; greater tuberosity of humerus</td>
<td>Axillary nerve</td>
<td>External rotation</td>
</tr>
<tr>
<td>Subscapularis</td>
<td>Scapula; lesser tuberosity of humerus</td>
<td>Subscapular nerve</td>
<td>Internal rotation and adduction</td>
</tr>
</tbody>
</table>

SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

Etiology

- impingement: “painful arc syndrome”, compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the undersurface of acromion, AC joint, and CA ligament
  - leads to bursitis, tendonitis, and if left untreated, can lead to rotator cuff thinning and tear
- anything that leads to a narrow subacromial space
  - glenohumeral muscle weakness leading to abnormal motion of humeral head
  - scapular muscle weakness leading to abnormal motion of acromion
  - acromial abnormalities such as congenital narrow space or osteophyte formation

Clinical Features
- night pain and difficulty sleeping on affected side
- pain worse with active motion; passive movement generally permitted
- weakness and loss of ROM especially between 90°-130° (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity
- rule out bicep tendinosis: Speed and Yergason’s tests; SLAP lesion: O’Brien’s test

Table 9. Rotator Cuff Special Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Examination</th>
<th>Positive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jobe’s Test</td>
<td>Supraspinatus: place the shoulder in 90° of abduction and 30° of forward flexion and internally rotate the arm so that the thumb is pointing toward the floor</td>
<td>Weakness with active resistance suggests a supraspinatus tear</td>
</tr>
<tr>
<td>Lift-off Test</td>
<td>Subscapularis: internally rotate arm so dorsal surface of hand rests on lower back; patient instructed to actively lift hand away from back against examiner resistance (use Belly Press Test if too painful)</td>
<td>Inability to actively lift hand away from back suggests a subscapularis tear</td>
</tr>
<tr>
<td>Posterior-Cuff Test</td>
<td>Infraspinatus and teres minor: arm positioned at patient’s side in 90° of flexion; patient instructed to externally rotate arm against the resistance of the examiner</td>
<td>Weakness with active resistance suggests posterior cuff tear</td>
</tr>
<tr>
<td>Neer’s Test</td>
<td>Rotator cuff impingement: passive shoulder flexion</td>
<td>Pain elicited between 130-170° suggests impingement</td>
</tr>
<tr>
<td>Hawkins-Kennedy Test</td>
<td>Rotator cuff impingement: shoulder flexion to 90° and passive internal rotation</td>
<td>Pain with internal rotation suggests impingement</td>
</tr>
<tr>
<td>Painful Arc Test</td>
<td>Rotator cuff tendinopathy: patient instructed to actively abduct the shoulder</td>
<td>Pain with abduction &gt; 90° suggests tendinopathy</td>
</tr>
</tbody>
</table>

Figure 15. Rotator cuff tests

Does this Patient with Shoulder Pain have Rotator Cuff Disease? The Rational Clinical Examination Systematic Review
JAMA 2013;310:837-847
Study: 5 studies of sufficient quality including 30-203 shoulders and a prevalence of RCD ranging from 33-81%.
Results/Conclusions: Among pain provocation tests, a positive painful arc test had the greatest specificity and sensitivity (SP 81%, SN 71%). Among strength tests, a positive external rotation lag test and internal rotation lag test were the most accurate for full-thickness tears (SP 47%, SN 94%; SP 97%, SN 83% respectively). The internal rotation lag test was therefore also the most accurate for identifying patients without a full-thickness tear. A positive drop arm test is helpful to identify patients with RCD (SN 24%, SP 93%).
Investigations
• x-rays: AP view may show high riding humerus relative to glenoid, evidence of chronic tendinitis
• MRI: coronal/sagittal oblique and axial orientations are useful for assessing full/partial tears and tendinopathy ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
• arthrogram: see full thickness tear, difficult to assess partial thickness tears

Treatment and Prognosis
• mild ("wear")
  ▪ treatment is non-operative (physiotherapy, NSAIDs)
• moderate ("tear")
  ▪ non-operative treatment ± steroid injection
• severe ("repair")
  ▪ impingement that is refractory to 2-3 mo physiotherapy and 1-2 injections
  ▪ may require arthroscopic or surgical repair, i.e. acromioplasty, rotator cuff repair

Acromioclavicular Joint Pathology

2 main ligaments attach clavicle to scapula: AC and CC ligaments

Mechanism
• fall onto shoulder with adducted arm (fall onto tip of shoulder)

Clinical Features
• palpate step deformity between distal clavicle and acromion (with dislocation)
• pain with adduction of shoulder and/or palpation over AC joint
• limited ROM

Investigations
• x-rays: AP, Zanca view (10-15° cephalic tilt), axillary ± stress views (10 lb weight in patient's hand)

Treatment
• non-operative (most common): sling 1-3 wk, ice, analgesia, rehabilitation
• operative
  ▪ indications: AC and CC ligaments are both torn and/or clavicle displaced posteriorly
  ▪ procedure: number of different approaches involving AC/CC ligament reconstruction or screw/hook plate insertion

Table 10. Rockwood Classification of Acromioclavicular Joint Separation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Joint sprain, absence of complete tear of either ligament</td>
<td>Non-operative</td>
</tr>
<tr>
<td>II</td>
<td>Complete tear of AC ligament, incomplete tear of CC ligament, without marked elevation of lateral clavicular head</td>
<td>Non-operative</td>
</tr>
<tr>
<td>III</td>
<td>Complete tear of AC and CC ligaments, &gt;5 mm elevation at AC joint, superior aspect of acromion is below the inferior aspect of the clavicle</td>
<td>Most non-operative, operative if laborer or high level athlete</td>
</tr>
<tr>
<td>IV/VI</td>
<td>Based on the anatomical structure the displaced clavicle is in proximity with</td>
<td>Operative in most cases</td>
</tr>
</tbody>
</table>

Clavicle Fracture

• incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
• common in children (unites rapidly without complications)

Mechanism
• fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

Clinical Features
• pain and tenting of skin
• arm is clasped to chest to splint shoulder and prevent movement

Treatment
• evaluate NVS of entire upper limb

Associated Injuries with Clavicle Fractures
• Up to 9% of clavicle fractures are associated with other fractures (most commonly rib fractures)
• Majority of brachial plexus injuries are associated with proximal third fractures
• medial and middle third clavicle fractures  
  ▪ figure-of-eight sling x 1-2 wk  
  ▪ early ROM and strengthening once pain subsides  
  ▪ if ends overlap >2 cm consider ORIF  
• distal third clavicle fractures  
  ▪ undisplaced (with ligaments intact): sling x 1-2 wk  
  ▪ displaced (CC ligament injury): ORIF  

**Specific Complications** (see General Fracture Complications, OR6)  
• cosmetic bump usually only complication  
• shoulder stiffness, weakness with repetitive activity  
• pneumothorax, brachial plexus injuries, and subclavian vessel (all very rare)  

# Frozen Shoulder (Adhesive Capsulitis)

**Definition**  
• disorder characterized by progressive pain and stiffness of the shoulder usually resolving spontaneously after 18 mo  

**Mechanism**  
• primary adhesive capsulitis  
  ▪ idiopathic, usually associated with DM  
  ▪ usually resolves spontaneously in 9-18 mo  
• secondary adhesive capsulitis  
  ▪ due to prolonged immobilization  
  ▪ shoulder-hand syndrome: CRPS/RSD characterized by arm and shoulder pain, decreased motion, and diffuse swelling  
  ▪ following MI, stroke, shoulder trauma  
  ▪ poorer outcomes  

**Clinical Features**  
• gradual onset (wk to mo) of diffuse shoulder pain with:  
  ▪ decreased active AND passive ROM  
  ▪ pain worse at night and often prevents sleeping on affected side  
  ▪ increased stiffness as pain subsides: continues for 6-12 mo after pain has disappeared  

**Investigations**  
• x-rays may be normal, or may show demineralization from disease  

**Treatment**  
• Freezing Phase  
  ▪ active and passive ROM (physiotherapy)  
  ▪ NSAIDs and steroid injections if limited by pain  
• Thawing Phase  
  ▪ manipulation under anesthesia and early physiotherapy  
  ▪ arthroscopy for debridement/decompression  

# Humerus

## Proximal Humeral Fracture

**Mechanism**  
• young: high energy trauma (MVC)  
• elderly: FOOSH from standing height in osteoporotic individuals  

**Clinical Features**  
• proximal humeral tenderness, deformity with severe fracture, swelling, painful ROM, bruising extends down arm later  

**Investigations**  
• test axillary nerve function (deltoid contraction and skin over deltoid)  
• x-rays: AP, trans-scapular, axillary are essential  
• CT scan: to evaluate for articular involvement and fracture displacement  

**Classification**  
• Neer classification is based on 4 fracture fragments (see Neer Classification sidebar, OR16)  
• displaced: displacement >1 cm and/or angulation >45°
• the Neer system regards displacement, not the fracture line, as meeting criteria for a ‘part’ in the classification scheme
• ± dislocated/subluxed: humeral head dislocated/subluxed from glenoid

**Treatment**
- treat osteoporosis if needed
- non-operative
  - nondisplaced - broad arm sling immobilization begin ROM in 7-10 d to prevent stiffness
  - minimally displaced - closed reduction with sling immobilization x 2 wk, gentle ROM
- operative
  - ORIF (anatomic neck fractures, displaced, associated dislocated glenohumeral joint)
  - hemiarthroplasty may be necessary, especially in elderly

**Specific Complications** (see General Fracture Complications, OR6)
- AVN, axillary nerve palsy, malunion, post-traumatic arthritis

---

**Humeral Shaft Fracture**

**Mechanism**
- direct blows/MVC (most common), FOOSH, twisting injuries, metastases (in elderly)

**Clinical Features**
- pain, swelling, ± shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment: look for drop wrist, sensory impairment dorsum of hand

**Investigations**
- x-rays: AP and lateral radiographs of the humerus including the shoulder and elbow joints

**Treatment**
- in general, humeral shaft fractures are treated non-operatively
- non-operative (most common)
  - ± reduction; can accept deformity due to compensatory ROM of shoulder
  - hanging cast (weight of arm in cast provides traction across fracture site) with collar and cuff sling immobilization until swelling subsides, then Sarmiento functional brace, followed by ROM
- operative
  - indications: open fracture, neurovascular injury, unacceptable fracture alignment, polytrauma, segmental fracture, pathological fracture, “floating elbow” (simultaneous unstable humeral and forearm fractures), intra-articular
  - ORIF: plating (most common), IM rod insertion, external fixation

**Specific Complications** (see General Fracture Complications, OR6)
- radial nerve palsy: expect spontaneous recovery in 3-4 mo, otherwise send for EMG
- non-union: most frequently seen in middle 1/3
- decreased ROM
- compartment syndrome

---

**Elbow**

**Supracondylar Fracture**

- most common in pediatric population (peak age ~7 yr old), rarely seen in adults
- fracture of the distal 1/3 of humerus just proximal to capitulum and trochlea, usually transverse
- AIN injury commonly associated with extension type

**Mechanism**
- >96% are extension injuries via FOOSH (e.g. fall off monkey bars); <4% are flexion injuries

**Clinical Features**
- pain, swelling, point tenderness
- neurovascular injury: assess median and radial nerves, radial artery (check radial pulse)

**Investigations**
- x-rays: AP, lateral of elbow
- disruption of anterior humeral line suggests supracondylar fracture

---

**Risk of radial nerve and brachial artery injury**

**Three Joints at the Elbow**
- Humeroradial joint
- Humeroulnar joint
- Radioulnar joint

---

**Figure 17. X-ray of transverse displaced supracondylar fracture of humerus with elbow dislocation**

**Normal carrying angle of elbow is ~10° of valgus**
Treatment
- reduction indications: evidence of arterial obstruction, unacceptable angulation, displaced (>50%)
- non-operative
  - nondisplaced: long arm plaster slab in 90° flexion x 3 wk
- operative
  - indications: displaced, vascular injury, open fracture
  - requires percutaneous pinning followed by limb cast with elbow flexed <90°
  - in adults, ORIF is necessary

Specific Complications (see General Fracture Complications, OR6)
- stiffness is most common
- brachial artery injury (kinking can occur if displaced fracture), median or ulnar nerve injury, compartment syndrome (leads to Volkmann’s ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)

Radial Head Fracture
- a common fracture of the upper limb in young adults

Mechanism
- FOOSH with elbow extended and forearm pronated

Clinical Features
- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, mechanical block to forearm pronation and supination
- pain on pronation/supination

Investigations
- x-ray: enlarged anterior fat pad ("sail sign") or the presence of a posterior fat pad indicates effusion which could occur with occult radial head fractures

Table 11. Classification and Treatment of Radial Head Fractures

<table>
<thead>
<tr>
<th>Mason Class</th>
<th>Radiographic Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nondisplaced fracture</td>
<td>Elbow slab or sling x 3-5 d with early ROM</td>
</tr>
<tr>
<td>2</td>
<td>Displaced fracture</td>
<td>ORIF if: angulation &gt;30°, involves ≥1/3 of the radial head, or if ≥3 mm of joint incongruity exists</td>
</tr>
<tr>
<td>3</td>
<td>Comminuted fracture</td>
<td>Radial head excision ± prosthesis</td>
</tr>
<tr>
<td>4</td>
<td>Comminuted fracture with posterior elbow dislocation</td>
<td>Radial head excision ± prosthesis</td>
</tr>
</tbody>
</table>

Specific Complications (see General Fracture Complications, OR6)
- myositis ossificans
- recurrent instability (if MCL injured and radial head excised)

Olecranon Fracture

Mechanism
- direct trauma to posterior aspect of elbow (fall onto the point of the elbow)

Clinical Features
- ≥ loss of active extension due to avulsion of triceps tendon

Investigations
- x-rays: AP + lateral (require true lateral to determine fracture pattern)

Treatment
- non-displaced (<2 mm, stable): cast x 3 wk (elbow in 90° flexion) then gentle ROM
- displaced: ORIF (plate and screws or tension band wiring) and early ROM if stable

Elbow Dislocation
- third most common joint dislocation after shoulder and patella
- usually the radius and ulna are dislocated together, or the radius head dislocates and the ulna remains ("Monteggia")
- anterior capsule and collateral ligaments disrupted
Mechanism
• elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion
• usually the radius and ulna are dislocated together, or the radius head dislocates and the ulna remains (“Monteggia”)
• 90% are posterior/posterolateral, anterior are rare and usually devastating

Clinical Features
• elbow pain, swelling, deformity
• flexion contracture
• ± absent radial or ulnar pulses

Treatment
• assess NVS before reduction: brachial artery, median and ulnar nerves (can become entrapped during manipulation)
• closed reduction under conscious sedation (post-reduction x-rays required)
• Parvin’s method: patient lies prone with arm hanging down; apply gentle traction downwards on wrist, as olecranon slips distally, gently lift up the arm at elbow to reduce joint
• long-arm splint with forearm in neutral rotation and elbow in 90° flexion
• early ROM (<2 wk)

Specific Complications (see General Fracture Complications, OR6)
• stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture
• recurrent instability uncommon

Epicondylitis
• lateral epicondylitis = “tennis elbow”, inflammation of the common extensor tendon as it originates from the lateral epicondylye
• medial epicondylitis = “golfer’s elbow”, inflammation of the common flexor tendon as it originates from the medial epicondylye

Mechanism
• repeated or sustained contraction of the forearm muscles/chronic overuse

Clinical Features
• point tenderness over humeral epicondyle and/or distal to it
• pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
• generally a self-limited condition, but may take 6-18 mo to resolve

Treatment
• rest, ice, NSAIDs
• use brace/strap
• physiotherapy, stretching, and strengthening
• corticosteroid injection
• surgery: percutaneous or open release of common tendon from epicondyle (only after 6-12 mo of conservative therapy)

Forearm

Radius and Ulna Fracture

Mechanism
• commonly a FOOSH or high-energy direct blow
• fractures usually accompanied by displacement due to high force

Investigations
• x-ray: 1) AP and lateral of forearm; 2) AP, lateral, oblique of elbow and wrist
• CT if fracture is close to joint

Treatment
• goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
• ORIF with plates and screws; closed reduction with immobilization usually yields poor results for displaced forearm fractures (except in children)

Complications (see General Fracture Complications, OR6)
• soft tissue contracture resulting in limited forearm rotation – surgical release of tissue may be warranted

In all isolated ulna fractures, assess proximal radius to rule out a Monteggia fracture
Monteggia Fracture

- more common and better prognosis in the pediatric age group when compared to adults

**Definition**
- fracture of the proximal ulna with radial head dislocation and proximal radioulnar joint injury

**Mechanism**
- direct blow on the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

**Clinical Features**
- decreased rotation of forearm ± palpable lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

**Treatment**
- adults: ORIF of ulna with indirect radius reduction in 90% of patients
- splint and early post-operative ROM if elbow completely stable, otherwise immobilization in plaster with elbow flexed for 6 wk
- pediatrics: attempt closed reduction and immobilization in plaster with elbow flexed for Bado Type I-III, surgery for Type IV

**Specific Complications** (see *General Fracture Complications, OR6*)
- PIN: most common nerve injury; observe for 3 mo as most resolve spontaneously
- radial head instability/redislocation
- radioulnar synostosis

Nightstick Fracture

**Definition**
- isolated fracture of ulna without dislocation of radial head

**Mechanism**
- direct blow to forearm (e.g. holding arm up to protect face)

**Treatment**
- non-displaced: below elbow cast (x 10 d) followed by forearm brace (~8 wk)
- displaced: ORIF if >50% shaft displacement or >10° angulation

Galeazzi Fracture

**Definition**
- fracture of the distal radial shaft with disruption of the DRUJ
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis
- 3x more common than Monteggia fracture

**Mechanism**
- hand FOOSH with axial loading of pronated forearm

**Investigations**
- x-rays
  - shortening of distal radius >5 mm relative to the distal ulna
  - widening of the DRUJ space on AP
  - dislocation of radius with respect to ulna on true lateral

**Treatment**
- ORIF of radius; afterwards assess DRUJ stability by balloting distal ulna relative to distal radius
- if DRUJ is stable and reducible, splint for 10-14 d with early ROM encouraged
- if DRUJ is unstable, ORIF or percutaneous pinning with long arm cast in supination x 6 wk

For all isolated radius fractures assess DRUJ to rule out a Galeazzi fracture
Wrist

Colles’ Fracture

Definition
• extra-articular transverse distal radius fracture (~2 cm proximal to the radiocarpal joint) with dorsal displacement ± ulnar styloid fracture

Epidemiology
• most common fracture in those >40 yr, especially in women and those with osteoporotic bone

Mechanism
• FOOSH

Clinical Features
• “dinner fork” deformity
• swelling, ecchymoses, tenderness

Investigations
• x-ray: AP and lateral wrist

Treatment
• goal is to restore radial height, radial inclination (22°), volar tilt (11°) as well as DRUJ stability and useful forearm rotation
• closed reduction (think opposite of the deformity):
  ▪ hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
  ▪ closed reduction: 1) traction with extension (exaggerate injury), 2) traction with ulnar deviation, pronation, flexion (of distal fragment – not at wrist)
  ▪ dorsal slab/below elbow cast for 5-6 wk
  ▪ x-ray x 1 wk for 3 wk and at cessation of immobilization to ensure reduction is maintained
• obtain post-reduction films immediately; repeat reduction if necessary, consider external fixation or ORIF if failure of adequate closed reduction

Smith’s Fracture

Definition
• volar displacement of the distal radius (i.e. reverse Colles’ fracture)

Mechanism
• fall onto the back of the flexed hand

Treatment
• usually unstable and needs ORIF
• if patient is poor operative candidate, may attempt non-operative treatment
• closed reduction with hematoma block (reduction opposite of Colles’)
• long-arm cast in supination x 6 wk

Complications of Wrist Fractures

• most common complications are poor grip strength, stiffness, and radial shortening
• distal radius fractures in individuals <40 yr of age are usually highly comminuted and are likely to require ORIF
• 80% have normal function in 6-12 mo

Table 12. Early and Late Complications of Wrist Fractures

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult reduction ± loss of reduction</td>
<td>Malunion, radial shortening</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Painful wrist secondary to ulnar prominence</td>
</tr>
<tr>
<td>Extensor pollicis longus tendon rupture</td>
<td>Frozen shoulder (“shoulder-hand syndrome”)</td>
</tr>
<tr>
<td>Acute carpal tunnel syndrome</td>
<td>Post-traumatic arthritis</td>
</tr>
<tr>
<td>Finger swelling with venous block</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Complications of a tight cast/splint</td>
<td>CRPS/ASD</td>
</tr>
</tbody>
</table>

Figure 23. Colles’ fracture and associated bony deformity

Figure 24. Normal wrist angles +
wrist angles in Colles’ fracture
Note the relative shortening of the radius relative to the ulna on AP view in Colles’ fracture
Scaphoid Fracture

Epidemiology
• common in young men; not common in children or in patients beyond middle age
• most common carpal bone injured
• may be associated with other carpal or wrist injuries (e.g. Colles’ fracture)

Mechanism
• FOOSH: impact of scaphoid on distal radius, most commonly resulting in a transverse fracture through the waist (65%), distal (10%), or proximal (25%) scaphoid

Clinical Features
• pain with wrist movement
• tenderness in the anatomical “snuff box”, over scaphoid tubercle, and pain with long axis compression into scaphoid
• usually nondisplaced

Investigations
• x-ray: PA, lateral, scaphoid views with wrist extension and ulnar deviation x 2 wk
• ± CT or MRI
• bone scan rarely used
• note: a fracture may not be radiologically evident up to 2 wk after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 wk later to rule out a fracture; if x-ray still negative order CT or MRI

Treatment
• early treatment critical for improving outcomes
• non-displaced (<1 mm displacement/<15° angulation): long-arm thumb spica cast x 4 wk then short arm cast until radiographic evidence of healing is seen (2-3 mo)
• displaced: ORIF with headless/countersink compression screw is the mainstay treatment, or percutaneous K-wire fixation (uncommon)

Specific Complications
• most common: non-union/mal-union (use bone graft from iliac crest or distal radius with fixation to heal)
• AVN of the proximal fragment
• delayed union (recommend surgical fixation)

Prognosis
• fractures of the proximal third of the scaphoid have 70% rate of non-union or AVN
• waist fractures have healing rates of 80-90%
• distal third fractures have healing rates close to 100%

Hand
• see Plastic Surgery, PL22

Spine

The proximal pole of the scaphoid receives as much as 100% of its arterial blood supply from the radial artery that enters at the distal radius. A fracture through the proximal third disrupts this blood supply and results in a high incidence of AVN/non-union

Figure 27. Schematic diagram of vertebral anatomy
Fractures of the Spine

- see Neurosurgery. NS32

Table 13. Fracture Type and Column Involvement

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Column Failure</th>
<th>Stable/Unstable</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression</td>
<td>Anterior</td>
<td>Stable</td>
<td>Compression</td>
</tr>
<tr>
<td>Burst</td>
<td>Anterior, middle</td>
<td>Unstable</td>
<td>High-energy axial loading + flexion</td>
</tr>
<tr>
<td>Fracture-Dislocation</td>
<td>Anterior, middle, posterior</td>
<td>Unstable</td>
<td>Significant force applied to spine (flexion, extension, distraction, rotation, shear or axial load)</td>
</tr>
<tr>
<td>Flexion-Distraction</td>
<td>Middle, posterior</td>
<td>± Unstable</td>
<td>MVC (lap belt only) causing flexion and distraction (Chance fracture)</td>
</tr>
</tbody>
</table>

Cervical Spine

General Principles
- C1 (atlas): no vertebral body, no spinous process
- C2 (axis): odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
- nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra), C8 nerve root exits below C7 vertebra
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord

Special Testing
- compression test: pressure on head worsens radicular pain
- distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain

Table 14. Cervical Radiculopathy/Neuropathy

<table>
<thead>
<tr>
<th>Root</th>
<th>C5 Motor</th>
<th>C6</th>
<th>C7 Motor</th>
<th>C8 Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deltoid</td>
<td>Biceps</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Interossei</td>
</tr>
<tr>
<td>Biceps</td>
<td>Brachioradialis</td>
<td>Vast flexion</td>
<td>Finger extension</td>
<td></td>
</tr>
<tr>
<td>Wrist extension</td>
<td></td>
<td></td>
<td></td>
<td>Digital flexors</td>
</tr>
<tr>
<td>Sensory</td>
<td>Auxillary nerve (patch over lateral deltoid)</td>
<td>Thumb and index finger</td>
<td>Middle finger</td>
<td>Ring and little finger</td>
</tr>
<tr>
<td>Reflex</td>
<td>Biceps</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Finger jerk</td>
</tr>
<tr>
<td></td>
<td>Brachioradialis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

X-Rays for C-Spine
- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- lateral
  - vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
  - angulation: between adjacent vertebral bodies (>11° is abnormal)
  - disc or facet joint widening
  - anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
  - oblique: evaluate pedicles and intervertebral foramen
  - ± swimmer’s view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
  - ± lateral flexion/extension view: evaluate subluxation of cervical vertebrae

Differential Diagnosis of C-Spine Pain
- neck muscle strain, cervical spondylosis, cervical stenosis, RA (spondylitis), traumatic injury, whiplash, myofascial pain syndrome

C-SPINE INJURY
- see Neurosurgery. NS33

Thoracolumbar Spine

General Principles
- spinal cord terminates at conus medullaris (L1)
- individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)
### Special Tests
- **straight leg raise:** passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down posterior/lateral leg to knee ± into foot
- **Lasegue maneuver:** dorsiflexion of foot during straight leg raise makes symptoms worse or, if leg is less elevated, dorsiflexion will bring on symptoms
- **femoral stretch test:** with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular symptoms of unilateral pain in lumbar region, buttock, or posterior thigh

#### Table 15. Lumbar Radiculopathy/Neuropathy

<table>
<thead>
<tr>
<th>Root</th>
<th>L4</th>
<th>L5</th>
<th>S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Quadriceps (knee extension + hip adduction)</td>
<td>Extensor hallucis longus (hip abduction)</td>
<td>Peroneus longus + brevis (ankle eversion)</td>
</tr>
<tr>
<td></td>
<td>Tibialis anterior (ankle inversion + dorsiflexion)</td>
<td>Gluteus medius (hip abduction)</td>
<td>Gastrocnemius + soleus (plantar flexion)</td>
</tr>
<tr>
<td>Sensory</td>
<td>Medial malleolus</td>
<td>1st dorsal webspace and lateral leg</td>
<td>Lateral foot</td>
</tr>
<tr>
<td>Reflex</td>
<td>Knee (patellar)</td>
<td>Medial hamstring*</td>
<td>Ankle (Achilles)</td>
</tr>
<tr>
<td>Test</td>
<td>Femoral stretch</td>
<td>Straight leg raise</td>
<td>Straight leg raise</td>
</tr>
</tbody>
</table>

*Unreliable

### Differential Diagnosis of Back Pain
1. **mechanical or nerve compression (>90%)**
   - degenerative (disc, facet, ligament)
   - peripheral nerve compression (disc herniation)
   - spinal stenosis (congenital, osteophyte, central disc)
   - cauda equina syndrome
2. **others (<10%)**
   - neoplastic (primary, metastatic, multiple myeloma)
   - infectious (osteomyelitis, TB)
   - metabolic (osteoporosis)
   - traumatic fracture (compression, distraction, translation, rotation)
   - spondyloarthropathies (ankylosing spondylitis)
   - referred (aorta, renal, ureter, pancreas)

### DEGENERATIVE DISC DISEASE
- loss of vertebral disc height with age results in:
  - bulging and tears of annulus fibrosus
  - change in alignment of facet joints
  - osteophyte formation
  - can cause back-dominant pain
- management
  - non-operative
    - staying active with modified activity
    - back strengthening
    - NSAIDs
  - do not treat with opioids; no proven efficacy of spinal traction or manipulation
  - operative – rarely indicated
    - decompression ± fusion
    - no difference in outcome between non-operative and surgical management at 2 yr

### Table 16. Types of Low Back Pain

<table>
<thead>
<tr>
<th>Mechanical Back Pain</th>
<th>Direct Nerve Root Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disc Origin</td>
<td>Facet Origin</td>
</tr>
<tr>
<td>Pain Dominance</td>
<td>Back</td>
</tr>
<tr>
<td>Aggravation</td>
<td>Flexion</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
</tr>
<tr>
<td>Duration</td>
<td>Long (wk, mo)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Relief of strain, exercise</td>
</tr>
</tbody>
</table>
SPINAL STENOSIS
- definition: narrowing of spinal canal <10 mm
- etiology: congenital (idiopathic, osteopetrosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylitis, Paget’s disease, trauma)
- clinical features
  - ± bilateral back and leg pain
  - neurogenic claudication
  - ± motor weakness
  - normal back flexion; difficulty with back extension
- investigations: CT/MRI reveals narrowing of spinal canal, but gold standard = CT myelogram
- treatment
  - non-operative: vigorous physiotherapy (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
  - operative: decompression surgery if conservative methods failed >6 mo

Table 17. Differentiating Claudication

<table>
<thead>
<tr>
<th></th>
<th>Neurogenic</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravation</td>
<td>With standing or exercise</td>
<td>Walking set distance</td>
</tr>
<tr>
<td></td>
<td>Walking distance variable</td>
<td></td>
</tr>
<tr>
<td>Alleviation</td>
<td>Change in position (usually flexion, sitting, lying down)</td>
<td>Stop walking</td>
</tr>
<tr>
<td>Time</td>
<td>Relief in ~10 min</td>
<td>Relief in ~2 min</td>
</tr>
<tr>
<td>Character</td>
<td>Neurogenic ± neurological deficit</td>
<td>Muscular cramping</td>
</tr>
</tbody>
</table>

Figure 30. Approach to back pain

MECHANICAL BACK PAIN
- definition: back pain NOT due to prolapsed disc or any other clearly defined pathology
- clinical features
  - dull backache aggravated by activity
  - morning stiffness
  - no neurological signs
- treatment: symptomatic (analgesics, physiotherapy)
- prognosis: symptoms may resolve in 4-6 wk, others become chronic

LUMBAR DISC HERNIATION
- definition: tear in annulus fibrosus allows protrusion of nucleus pulposus causing either a central, posterolateral, or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
- etiology: usually a history of flexion-type injury
- clinical features
  - back dominant pain (central herniation) or leg dominant pain (lateral herniation)
  - tenderness between spinous processes at affected level
  - muscle spasm ± loss of normal lumbar lordosis
  - neurological disturbance is segmental and varies with level of central herniation
    - motor weakness (L4, L5, S1)
    - diminished reflexes (L4, S1)
    - diminished sensation (L4, L5, S1)
  - positive straight leg raise
  - positive Lasegue test
  - bowel or bladder symptoms, decreased rectal tone suggests cauda equina syndrome due to central disc herniation – surgical emergency
- investigations: MRI, consider a post-void residual volume to check for urinary retention; post-void >100 mL should heighten suspicion for cauda equina syndrome
- treatment
• symptomatic
  • extension protocol (physiotherapy)
  • NSAIDs
  • 90% resolve in 3 mo; surgical discectomy reserved for progressive neurological deficit, failure of symptoms to resolve within 3 mo, or cauda equina syndrome due to central disc herniation

**SPONDYLOLYSIS**
- definition: defect in the pars interarticularis with no movement of the vertebral bodies
- etiology
  - trauma: gymnasts, weightlifters, backpackers, loggers, laborers
- clinical features: activity-related back pain, pain with unilateral extension (Michelis’ test)
- investigations
  - oblique x-ray: “collar” break in the “Scottie dog’s” neck
  - bone scan
  - CT scan
- treatment: activity restriction, brace, stretching exercise

**SPONDYLOLISTHESIS**
- definition: defect in pars interarticularis causing a forward slip of one vertebra on another usually at L5-S1, less commonly at L4-5
- etiology: congenital (children), degenerative (adults), traumatic, pathological, teratogenic
- clinical features: lower back pain radiating to buttocks

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage of Slip</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-25%</td>
<td>Symptomatic operative fusion only for intractable pain</td>
</tr>
<tr>
<td>2</td>
<td>25-50</td>
<td>Same as above</td>
</tr>
<tr>
<td>3</td>
<td>50-75</td>
<td>Decompression for spondylolisthesis and spinal fusion</td>
</tr>
<tr>
<td>4</td>
<td>75-100</td>
<td>Same as above</td>
</tr>
<tr>
<td>5</td>
<td>&gt;100</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

**Specific Complications**
- may present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

# Pelvis

## Pelvic Fracture

**Mechanism**
- young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- elderly: fall from standing height, low energy trauma
- lateral compression (most common), vertical shear, or anteroposterior compression fractures

**Clinical Features**
- local swelling, tenderness
- deformity of lower extremity
- pelvic instability

**Investigations**
- x-ray: AP pelvis, inlet and outlet views, Judet views (obturator and iliac oblique for acetabular fracture)
  - 6 cardinal radiographic lines of the acetabulum: ilioischial line, iliopectineal line, tear drop, roof, posterior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture

### Possible Radiological Findings:
- Pubic rami fractures: superior/inferior
- Pubic symphysis diastasis: common in AP compression (N=6 mm)
- Sacral fractures: common in lateral compression
- SI joint diastasis: common in AP compression (N=1-4 mm)
- Disrupted anterior column (iliopectineal line) or posterior column (ilioischial line)
  - “Teardrop” displacement: acetabular fracture
  - Iliac, ischial avulsion fractures
  - Displacement of the major fragment: superior (VS), open book (APC), bucket handle (LC)
Classification

Table 19. Tile Classification of Pelvic Fractures (see Figure 34)

<table>
<thead>
<tr>
<th>Type</th>
<th>Stability</th>
<th>Description</th>
</tr>
</thead>
</table>
| A    | Rotationally stable | A1: fracture not involving pelvic ring  
Vertically stable | A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture) |
| B    | Rotationally unstable | B1: open book  
Vertically stable | B2: lateral compression – ipsilateral  
B3: lateral compression – contralateral |
| C    | Rotationally unstable | C1: unilateral  
Vertically unstable | C2: bilateral  
C3: associated acetabular fracture |

Treatment

- ABCDEs
- assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)  
  - if involved, the fracture is considered an open fracture
- stable fractures: non-operative treatment, protected weight bearing
- emergency management  
  - IV fluids/blood  
  - pelvic binder/sheeting  
  - external fixation vs. emergent angiography/embolization  
  - ± laparotomy (if FAST/DPL positive)
- indications for operative treatment  
  - unstable pelvic ring injury  
  - disruption of anterior and posterior SI ligament  
  - symphysis diastasis >2.5 cm  
  - vertical instability of the posterior pelvis

Specific Complications (see General Fracture Complications, OR6)

- hemorrhage (life-threatening)
- injury to rectum or urogenital structures
- obstetrical difficulties, sexual and voiding dysfunction
- persistent SI joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high risk of DVT/PE

Hip

Hip Dislocation

- full trauma survey (see Emergency Medicine, Initial Patient Assessment/Management, ER2)
- examine for neurovascular injury PRIOR to open or closed reduction
- reduce hip dislocations ASAP (ideally within 6 h) to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 wk post-reduction
- see Hip Dislocation after Total Hip Arthroplasty, OR28

ANTERIOR HIP DISLOCATION

- mechanism: posteriorly directed blow to knee with hip widely abducted
- clinical features: shortened, abducted, externally rotated limb
- treatment  
  - closed reduction under conscious sedation/GA  
  - post-reduction CT to assess joint congruity

POSTERIOR HIP DISLOCATION

- most frequent type of hip dislocation
- mechanism: severe force to knee with hip flexed and adducted  
  - e.g. knee into dashboard in MVC
- clinical features: shortened, adducted, internally rotated limb
- treatment  
  - closed reduction under conscious sedation/GA only if associated femoral neck fracture  
  - ORIF if unstable, intra-articular fragments or posterior wall fracture  
  - post-reduction CT to assess joint congruity and fractures  
  - if reduction is unstable, put in traction x 4-6 wk

Rochester Method to Reduce Dislocations

- Patient lying supine with hip and knee flexed on injured side
- Surgeon stands on patient’s injured side
- Surgeon passes one arm under patient’s flexed knee, reaching to place that hand on patient’s other knee (thus supporting patient’s injured leg)
- With other hand, surgeon grasps patient’s ankle on injured side, applying traction, while assistant stabilizes pelvis  
  - Reduction via traction, internal rotation, then external rotation once femoral head clears acetabular rim

Figure 35. Rochester method
CENTRAL HIP DISLOCATION (rare)
• traumatic injury where femoral head is pushed medially through acetabulum

COMPLICATIONS FOR ALL HIP DISLOCATIONS
• post-traumatic OA
• AVN of femoral head
• fracture of femoral head, neck, or shaft
• sciatic nerve palsy in 25% (10% permanent)
• HO
• thromboembolism – DVT/PE

Hip Fracture

General Features
• acute onset of hip pain
• unable to weight-bear
• shortened and externally rotated leg
• painful ROM

Table 20. Overview of Hip Fractures

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Definition</th>
<th>Mechanism</th>
<th>Special Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Neck</td>
<td>Intracapsular (See Garden Classification, Table 21)</td>
<td>Young: MVC, fall from height; Elderly: fall from standing, rotational force</td>
<td>Same as general</td>
<td>X-ray: hip, pelvis, cross table lateral hip</td>
<td>Closed reduction under fluoroscopy then dynamic hip screw or IM nail</td>
<td>DVT, non-union, AVN</td>
</tr>
<tr>
<td>Intertrochanteric fracture Stable: intact posteromedial cortex Unstable: non-intact posteromedial cortex</td>
<td>Extracapsular fracture including the greater and lesser trochanters and transitional bone between the neck and shaft</td>
<td>Same as femoral neck fracture Direct or indirect force transmitted to the intertrochanteric area</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-ray: pelvis, AP/lateral hip</td>
<td>Closed reduction under fluoroscopy then dynamic hip screw or IM nail</td>
<td>DVT, varus displacement of proximal fragment, malrotation, non-union, failure of fixation device</td>
</tr>
<tr>
<td>Subtrochanteric fracture</td>
<td>Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft</td>
<td>Young: high energy trauma Elderly: osteopenic bone + fall, pathological fracture</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-ray: pelvis, AP/lateral hip and femur</td>
<td>Closed/open under fluoroscopy then plate fixation or IM nail</td>
<td>Malalignment, non-union, wound infection</td>
</tr>
</tbody>
</table>

Table 21. Garden Classification of Femoral Neck Fractures

<table>
<thead>
<tr>
<th>Type</th>
<th>Displacement</th>
<th>Extent</th>
<th>Alignment</th>
<th>Trabeculae</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>“Incomplete”</td>
<td>Valgus or neutral</td>
<td>Malaligned</td>
<td>Internal fixation to prevent displacement (valgus impacted fracture)</td>
</tr>
<tr>
<td>II</td>
<td>None</td>
<td>Complete</td>
<td>Neutral</td>
<td>Aligned</td>
<td>Internal fixation to prevent displacement</td>
</tr>
<tr>
<td>III</td>
<td>Some</td>
<td>Complete</td>
<td>Varus</td>
<td>Malaligned</td>
<td>Young: ORIF Elderly: hemi-total hip arthroplasty</td>
</tr>
<tr>
<td>IV</td>
<td>Complete</td>
<td>Complete</td>
<td>Varus</td>
<td>Aligned</td>
<td>Young: ORIF Elderly: hemi-total hip arthroplasty</td>
</tr>
</tbody>
</table>

AVN of Femoral Head
• Distal to proximal blood supply along femoral neck to head (medial and lateral femoral circumflex arteries)
• Susceptible to AVN if blood supply disrupted
• Etiology: femoral neck fracture, chronic systemic steroid use, SCFE, Legg-Calvé-Perthes, SLE, RA
Arthritis of the Hip

Etiology
- OA, inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders, or septic arthritis

Clinical Features
- pain (groin, medial thigh) and stiffness aggravated by activity
- morning stiffness >1 h, multiple joint swelling, hand nodules (RA)
- decreased ROM (internal rotation is lost first)
- crepitus
- ± fixed flexion contracture leading to apparent limb shortening (Thomas test)
- ± Trendelenberg sign

Investigations
- x-ray
  - OA: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes
  - RA: osteopenia, erosion, joint space narrowing, subchondral cysts, symmetric joint space narrowing
- blood work: ANA, RF

Treatment
- non-operative: weight reduction, activity modification, physiotherapy, analgesics, walking aids
- operative: realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
- complications with arthroplasty: component loosening, dislocation, HO, thromboembolism, infection, neurovascular injury, limb length discrepancy
- arthroplasty is standard of care in most patients with hip arthritis

Hip Dislocation after Total Hip Arthroplasty

Etiology
- THA that is unstable when hip is flexed, adducted and internally rotated, or extended and externally rotated (avoid flexing hip >90° or crossing legs for ~6 wk after surgery)

Epidemiology
- occurs in 1-4% of primary THA and 10-16% of revision THAs
- risk factors: neurological impairment, post-traumatic arthritis, revision surgery, substance abuse

Treatment
- external abduction splint to prevent hip adduction
- constrained acetabular component for recurrent dislocation if no issue with position of acetabular/femoral implants + knee immobilizer

Complications
- sciatic nerve palsy in 25% (10% permanent)
- HO

DVT Prophylaxis in Elective THA (continue 10-35 d post-operative)
Fondaparinux, low molecular weight heparin, or coumadin

Figure 37. Garden classification of femoral neck fractures

Figure 38. Distal femoral fractures
Femur

Femoral Diaphysis Fracture

Mechanism
• high energy trauma (MVC, fall from height, gunshot wound)
• in children, can result from low energy trauma (spiral fracture)

Clinical Features
• shortened, externally rotated leg (if fracture displaced)
• inability to weight-bear
• often open injury, always a Gustilo III (see Table 5, OR9)

Investigations
• AP pelvis, AP/lateral hip, femur, knee

Complications
• hemorrhage requiring transfusion
• fat embolism leading to ARDS
• extensive soft tissue damage
• ipsilateral hip dislocation/fracture (2-6%)
• nerve injury

Treatment
• stabilize patient
• immobilize leg
• ORIF with anterograde or retrograde IM nail, external fixator for unstable patients, open fractures, or highly vascular areas, or plate and screws for open growth plates within 24 h
• early mobilization and strengthening

Distal Femoral Fracture

Mechanism
• direct high energy force or axial loading
• three types in addition to classification as intra-articular or extra-articular

Clinical Features
• extreme pain
• knee effusion (hemarthrosis)
• shortened, externally rotated leg if displaced
• neurovascular deficits can occur with displaced fracture

Treatment
• ORIF if displaced or intra-articular; may choose to manage non-operatively if nondisplaced or incomplete fracture
• early mobilization and strengthening

Complications (see General Fracture Complications, OR6)
• femoral artery tear
• popliteal artery injury
• nerve injury
• extensive soft tissue injury
• angulation deformities

It is important to rule out ipsilateral femoral neck fracture as they occur in 2-6% of femoral diaphysis fractures and are reportedly missed in 19-31% of cases.
Knee

Evaluation of Knee

Common Complaints
- general orthopedic history
- also inquire about common knee symptoms
  - locking: mechanical block to extension
  - torn meniscus/loose body in joint
  - pseudo-locking: limited ROM without mechanical block
  - effusion, muscle spasm after injury, arthritis
  - painful clicking (audible)
  - torn meniscus
  - giving way: instability
  - cruciate ligament or meniscal tear, patellar dislocation

Special Tests of the Knee
- anterior and posterior drawer tests
  - demonstrate ACL and PCL, respectively
  - knee flexed at 90°, foot immobilized, hamstrings released
  - if able to sublux tibia anteriorly (anterior drawer test), then ACL may be torn
  - if able to sublux tibia posteriorly (posterior drawer test), then PCL may be torn
- Lachmann test
  - demonstrates torn ACL
  - hold knee in 10-20° flexion, stabilizing the femur
  - try to sublux tibia anteriorly on femur
  - similar to anterior drawer test, more reliable due to less muscular stabilization
  - for ACL: 25.0 positive likelihood ratio, 0.1 negative likelihood ratio
- Thessaly test
  - demonstrates meniscal tear
  - patient stands flat footed on one leg while the examiner provides his or her hands for balance. The patient then flexes the knee to 20° and rotates the femur on the tibia medially and laterally three times while maintaining the 20° flexion
  - positive for a meniscal tear if the patient experiences medial or lateral joint line discomfort
  - for medial meniscus: 29.67 positive likelihood ratio, 0.11 negative likelihood ratio
  - for lateral meniscus: 23.0 positive likelihood ratio, 0.083 negative likelihood ratio
- posterior sag sign
  - demonstrates torn PCL
  - may give a false positive anterior draw sign
  - flex knees and hips to 90°, hold ankles and knees
  - view from the lateral aspect
  - if one tibia sags posteriorly compared to the other, its PCL is torn
- pivot shift sign
  - demonstrates torn ACL
  - start with the knee in extension
  - internally rotate foot, slowly flex knee while palpating and applying a valgus force
  - normal knee will flex smoothly
  - if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the “pivot”)
  - reverse pivot shift (start in flexion, externally rotate, apply valgus and extend knee) suggests torn PCL
  - composite assessment for ACL: 25.0 positive likelihood ratio, 0.04 negative likelihood ratio
  - composite assessment for PCL: 21.0 positive likelihood ratio, 0.05 negative likelihood ratio
- collateral ligament stress test
  - palpate ligament for “opening” of joint space while testing
  - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
  - repeat tests with knee in 20° flexion to relax joint capsule
  - opening only in 20° flexion due to MCL damage only
  - opening in 20° of flexion and full extension is due to MCL, cruciate, and joint capsule damage
- tests for meniscal tear
  - joint line tenderness
  - joint line pain when palpated
  - palpate one side at a time and watch patient’s eyes
  - for meniscal tear: 0.9 positive likelihood ratio, 1.1 negative likelihood ratio
  - crouch compression test
    - joint line pain when squatting (anterior pain suggests patellofemoral pathology)
McMurray’s test useful collaborative information:
- with knee in flexion, palpate joint line for painful “pop/click”
- internally rotate foot, varus stress, and extend knee to test lateral meniscus
- externally rotate foot, valgus stress, and extend knee to test medial meniscus
- for meniscal tear: 1.3 positive likelihood ratio, 0.8 negative likelihood ratio
- composite assessment for meniscal tears: 2.7 positive likelihood ratio, 0.4 negative likelihood ratio

X-Rays
- AP standing, lateral
- skyline: tangential view with knees flexed at 45° to see patellofemoral joint
- 3-foot standing view: useful in evaluating leg length and varus/valgus alignment
- Ottawa Knee Rules (see Emergency Medicine, ER17)

Cruciate Ligament Tears

- ACL tear much more common than PCL tear

Table 22. Comparison of ACL and PCL Injuries

<table>
<thead>
<tr>
<th></th>
<th>Anterior Cruciate Ligament</th>
<th>Posterior Cruciate Ligament</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy</strong></td>
<td>From medial wall of lateral femoral condyle to the anteromedial and posterolateral intercondylar eminence of the tibial plateau</td>
<td>Lateral wall of medial femoral condyle to posterior intercondylar eminence of the tibial plateau</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Sudden deceleration Hyperextension and internal rotation of tibia on femur (i.e. “plant and turn”)</td>
<td>Sudden posterior displacement of tibia when knee is flexed or hyperextended (e.g. dashboard MVC injury)</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Audible “pop” Immediate swelling Knee “giving way” Inability to continue activity</td>
<td>Audible “pop” Immediate swelling Pain with push off Cannot descend stairs</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td>Effusion (hemarthrosis) Posterior lateral joint line tenderness Positive anterior drawer Positive Lachmann Pivot shift Test for MCL, meniscal injuries</td>
<td>Effusion (hemarthrosis) Anteromedial joint line tenderness Positive posterior drawer Reverse pivot shift Other ligamentous, bony injuries</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Stable knee with minimal functional impairment: immobilization 2-4 wk with early ROM and strengthening</td>
<td>Unstable knee or young person/high-demand lifestyle: ligament reconstruction Posterior sag</td>
</tr>
</tbody>
</table>

Collateral Ligament Tears

Mechanism
- valgus force to knee = MCL tear
- varus force to knee = LCL tear

Clinical Features
- swelling/effusion
- tenderness above and below joint line medially (MCL) or laterally (LCL)
- joint laxity with varus or valgus force to knee
- laxity with endpoint suggests partial tear
- laxity with no endpoint suggests a complete tear
- test for other injuries (e.g. O’Donoghue’s unhappy triad), common peroneal nerve injury

Treatment
- partial tear: immobilization x 2-4 wk with early ROM and strengthening
- complete tear: immobilization at 30° flexion
- multiple ligamentous injuries: surgical repair of ligaments
**Meniscal Tears**

- **Mechanism**
  - twisting force on knee when it is partially flexed (e.g. stepping down and turning)
  - requires moderate trauma in young person but only mild trauma in elderly due to degeneration

- **Clinical Features**
  - immediate pain, difficulty weight-bearing, instability, and clicking
  - increased pain with squatting and/or twisting
  - effusion (hemarthrosis) with insidious onset (24-48 h after injury)
  - joint line tenderness medially or laterally
  - locking of knee (if portion of meniscus mechanically obstructing extension)

- **Investigations**
  - MRI, arthroscopy

- **Treatment**
  - if not locked: ROM and strengthening (NSAIDs)
  - if locked or failed above: arthroscopic repair/partial meniscectomy

---

**Quadiceps/Patellar Tendon Rupture**

- **Mechanism**
  - sudden forceful contraction of quadriceps during an attempt to stop
  - more common in obese patients and those with pre-existing degenerative changes in tendon
    - DM, SLE, RA, steroid use, renal failure on dialysis

- **Clinical Features**
  - inability to extend knee or weight-bear
  - possible audible “pop”
  - patella in lower or higher position with palpable gap above or below patella respectively
  - may have an effusion

- **Investigations**
  - ask patient to straight leg raise
  - knee x-ray to rule out patellar fracture
  - lateral view: patella alta with patella tendon rupture, patella baja (infera) with quadriceps tendon rupture

- **Treatment**
  - non-operative treatment for incomplete tears with preserved extension of knee
  - surgical repair of tendon indicated for complete ruptures
  - early surgical repair: better outcomes compared with delayed repair (>6 wk post injury)
  - delayed repair complicated by quadriceps contracture, patella migration, and adhesions

---

**Dislocated Knee**

- **Mechanism**
  - high energy trauma
  - by definition, caused by tears of multiple ligaments

- **Clinical Features**
  - classified by relation of tibia with respect to femur
    - anterior, posterior, lateral, medial, rotary
  - knee instability
  - effusion
  - pain
  - ischemic limb

- **Investigations**
  - x-rays: AP, lateral, skyline
    - associated radiographic findings include tibial plateau fracture dislocations, proximal fibular fractures, and avulsion of fibular head
  - ankle brachial index (abnormal if <0.9)
  - arteriogram or CT angiogram if abnormal vascular exam (such as abnormal pedal pulses)
Treatment
- urgent closed reduction
  - complicated by interposed soft tissue
- assessment of peroneal nerve, tibial artery, and ligamentous injuries
- repair of associated injuries; also may need decompressive fasciotomy especially if vascular repair undertaken
- knee immobilization x 6-8 wk

Specific Complications
- high incidence of associated injuries
  - popliteal artery tear
  - peroneal nerve injury
  - capsular tear
- chronic: instability, stiffness, post-traumatic arthritis

Patella

Patellar Fracture

Mechanism
- direct blow to the patella: fall, MVC (dashboard)
- indirect trauma by sudden flexion of knee against contracted quadriceps

Clinical Features
- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- ± effusion/hemarthrosis

Investigations
- x-rays: AP, lateral, skyline
- do not confuse with bipartite patella: congenitally unfused ossification centers with smooth margins on x-ray at superolateral corner

Treatment
- goal: restore extensor mechanism with maximal articular congruency
- non-displaced (step-off <2-3 mm and fracture gap <1-4 mm)
  - straight leg immobilization 1-4 wk with hinged knee brace, weight bearing as tolerated
  - progress in flexion after 2-3 wk
  - physiotherapy: quadriceps strengthening when pain has subsided
- displaced: ORIF (>2 mm)
- comminuted: ORIF; may require partial/complete patellectomy
- disrupted extensor mechanism: ORIF

Patellar Dislocation

Mechanism
- usually a non-contact twisting injury
- lateral displacement of patella after contraction of quadriceps at the start of knee flexion in an almost straight knee joint
- direct blow, e.g. knee/helmet to knee collision

Risk Factors
- young, female
- obesity
- high-riding patella (patella alta)
- knock-knees (genu valgus)
- Q-angle (quadriceps angle) ≥20°
- shallow intercondylar groove
- weak vastus medialis
- tight lateral retinaculum
- ligamentous laxity (Ehlers-Danlos)

Clinical Features
- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced

Complications
- Symptomatic wiring
- Loss of reduction
- Osteonecrosis (proximal fragment)
- Hardware failure
- Knee stiffness
- Nonunion
- Infection

Figure 44. Types of patellar fractures

Figure 45. Q-angle
The angle between a vertical line through the patella and tibial tuberosity and a line from the ASIS to the middle patella. The larger the angle the greater the amount of lateral force on the knee (normal <20°)
• positive patellar apprehension test
  ▪ passive lateral translation results in guarding and patient apprehension
• often recurrent, self-reducing
• concomitant MCL injury

Investigations
• x-rays: AP, lateral, skyline view of patella
  ▪ check for fracture of medial patella (most common) and lateral femoral condyle

Treatment
• non-operative first
  ▪ NSAIDS, activity modification, and physical therapy
  ▪ short-term immobilization for comfort then 6 wk controlled motion
  ▪ progressive weight bearing and isometric quadriceps strengthening
• if recurrent or if loose bodies present
  ▪ surgical tightening of medial capsule and release of lateral retinaculum, possible tibial tuberosity transfer, or proximal tibial osteotomy

Patellofemoral Syndrome (Chondromalacia Patellae)

Mechanism
• softening, erosion and fragmentation of articular cartilage, predominantly medial aspect of patella
• commonly seen in active young females

Predisposing Factors
• malalignment causing patellar maltracking (Q angle ≥20°, genu valgus)
• post-trauma
• deformity of patella or femoral groove
• recurrent patellar dislocation, ligamentous laxity
• excessive knee strain (athletes)

Clinical Features
• deep, aching anterior knee pain
  ▪ exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting or kneeling
• insidious onset and vague in nature
• sensation of instability, pseudolocking
• pain with extension against resistance through terminal 30-40°
• pain with compression of patella with knee ROM
• swelling rare, minimal if present
• palpable crepitus

Investigations
• x-rays: AP, lateral, skyline

Treatment
• non-operative
  ▪ continue non-impact activities; rest and rehabilitation
  ▪ NSAIDs
  ▪ physiotherapy: vastus medialis and core strengthening
• surgical with refractory patients
  ▪ tibial tubercle elevation
  ▪ arthroscopic shaving/debridement
  ▪ lateral release of retinaculum

Pain with firm compression of patella into medial femoral groove is pathognomonic of patellofemoral syndrome.
**Tibia**

### Tibial Plateau Fracture

**Mechanism**
- varus/valgus load ± axial loading (e.g. fall from height)
- femoral condyles driven into proximal tibia
- can result from minor trauma in osteoporotics

**Clinical Features**
- frequency: lateral > medial
- medial fractures require higher energy – often have concomitant vascular injuries
- knee effusion
- inability to bear weight
- swelling
- associated with compartment syndrome

**Classification**
- Schatzker classification

**Investigations**
- x-rays: AP, lateral, oblique
- CT: pre-operative planning, identify articular depression and comminution

**Treatment**

<table>
<thead>
<tr>
<th>Approach #1 (based on amount of depression seen on x-ray)</th>
<th>Approach #2 (based on varus/valgus instability)</th>
</tr>
</thead>
<tbody>
<tr>
<td>If depression on x-ray is &lt;3 mm: Straight leg immobilization x 4-6 wk with progressive ROM weight bearing</td>
<td>If minimal varus/valgus instability (&lt;15°): Straight leg immobilization x 4-6 wk with progressive ROM weight bearing</td>
</tr>
<tr>
<td>ORIF often requiring bone grafting to elevate depressed fragment</td>
<td></td>
</tr>
</tbody>
</table>

**Specific Complications** (see General Fracture Complications, OR6)
- ligamentous injuries
- meniscal lesions
- AVN
- infection
- OA

### Tibial Shaft Fracture

**Mechanism**
- low energy pattern: torsional injury
- high energy: including MVC, falls, sporting injuries

**Clinical Features**
- open vs. closed
- amount of displacement
- NVS
- most commonly fractured long bone
- most common open fracture

**Investigations**
- x-rays: AP, lateral, skyline
  - full length, plus knee and ankle

**Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>closed minimally displaced: straight leg cast x 4 wk, functional brace after</td>
</tr>
<tr>
<td>displaced: ORIF with reamed IM nail, plate and screws, or external fixator</td>
</tr>
<tr>
<td>open</td>
</tr>
<tr>
<td>antibiotics, I&amp;D</td>
</tr>
<tr>
<td>external fixation or IM nail</td>
</tr>
<tr>
<td>vascularized coverage of soft tissue defects (often heal poorly)</td>
</tr>
</tbody>
</table>

**Specific Complications** (see General Fracture Complications, OR6)
- high incidence of neurovascular injury and compartment syndrome
- poor soft tissue coverage (critical to outcome)

---

**Schatzker Classification**

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of lateral plateau split fracture</td>
</tr>
<tr>
<td>II</td>
<td>Lateral split-depressed fracture</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lateral plateau: pure depression fracture</td>
</tr>
<tr>
<td>IV</td>
<td>Medial plateau fracture</td>
</tr>
<tr>
<td>V</td>
<td>Bicondylar plateau fracture</td>
</tr>
<tr>
<td>VI</td>
<td>Bicondylar with metaphyseal/diaphyseal involvement</td>
</tr>
</tbody>
</table>

---

**Low Molecular Weight Heparin for Prevention of Venous Thromboembolism in Patients with Lower-Leg Immobilization**

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Cochrane DB Syst Rev 2014;4:CD006681</th>
</tr>
</thead>
<tbody>
<tr>
<td>To evaluate the effectiveness of LMWH as VTE prophylaxis in patients with lower-leg immobilization in an ambulant setting.</td>
<td></td>
</tr>
<tr>
<td><strong>Selection Criteria</strong>: RCTs and CCTs comparing LMWH to no prophylaxis or placebo in patients immobilized with a plaster cast or brace.</td>
<td></td>
</tr>
<tr>
<td><strong>Results/Conclusions</strong>: 6 RCTs, 1,490 patients. Incidence of VTE was 4.3-40% in patients immobilized for &gt;1 wk without thromboprophylaxis or with placebo. With daily LMWH subcutaneous injections, incidence was 0-37% (OR 0.49, 95% CI 0.34-0.72). There were no reports of heparin-induced thrombocytopenia. The use of LMWH in outpatients with lower-leg immobilization significantly reduces the number of VTE events.</td>
<td></td>
</tr>
</tbody>
</table>
Ankle

Evaluation of Ankle and Foot Complaints

Special Tests
- anterior drawer: examiner attempts to displace the foot anteriorly against a fixed tibia
- talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated by x-ray

X-Ray
- AP, lateral
- mortise view: ankle at 15° of internal rotation
  - gives true view of ankle joint
  - joint space should be symmetric with no talar tilt
- Ottawa Ankle Rules should guide use of x-ray; nearly 100% sensitivity
- ± CT to better characterize fractures

Ankle Fracture

Mechanism
- pattern of fracture depends on the position of the ankle when trauma occurs
- generally involves
  - ipsilateral ligamentous tears or transverse bony avulsion
  - contralateral shear fractures (oblique or spiral)
- classification systems
  - Danis-Weber
  - Lauge-Hansen: based on foot's position and motion relative to leg

Danis-Weber Classification
- based on level of fibular fracture relative to syndesmosis
  - Type A (infra-syndesmotic)
    - pure inversion injury
    - avulsion of lateral malleolus below plafond or torn calcaneofibular ligament
    - ± shear fracture of medial malleolus
  - Type B (trans-syndesmotic)
    - external rotation and eversion (most common)
    - ± avulsion of medial malleolus or rupture of deltoid ligament
    - spiral fracture of lateral malleolus starting at plafond
  - Type C (supra-syndesmotic)
    - pure external rotation
    - avulsion of medial malleolus or torn deltoid ligament
    - ± posterior malleolar avulsion with posterior tibio-fibular ligament
    - fibular fracture is above plafond (called Maisonneuve fracture if at proximal fibula)
    - frequently tears syndesmosis

Treatment
- undisplaced: NWB below knee cast
- indications for ORIF
  - any fracture-dislocation: restore vascularity, minimize articular injury, reduce pain and skin pressure
  - most of type B, and all of type C
  - talar tilt >10°
  - medial clear space on x-ray greater than superior clear space
  - open fracture/open joint injury
- high incidence of post-traumatic arthritis
- wrinkle test: skin shows wrinkles, to determine if soft tissue swelling has resolved to an extent to reduce complications

Ligamentous Injuries

- see Figure 48 for ankle ligaments

Medial Ligament Complex (deltoid ligament)
- eversion injury
- usually avulses medial or posterior malleolus and strains syndesmosis

Ottawa Ankle Rules (see Emergency Medicine, ER17)
X-rays are only required if:
- Pain in the malleolar zone AND bony tenderness over the posterior aspect of the medial or lateral malleolus OR inability to weight bear both immediately after injury and in the ER

With a history of trauma from axial loading of lower limb always consider spinal injuries, femoral neck, tibial plateau, and talus/calcaneal fractures
Lateral Ligament Complex (Anterior Talofibular, Calcaneofibular, Posterior Talofibular)
- inversion injury, >90% of all ankle sprains
- ATF most commonly and severely injured if ankle is plantar flexed
- swelling and tenderness anterior to lateral malleolus
- ++ ecchymoses
- positive ankle anterior drawer
- may have significant medial talar tilt on inversion stress x-ray

Treatment
- microscopic tear (Grade I)
  - rest, ice, compression, elevation (RICE)
- macroscopic tear (Grade II)
  - strap ankle in dorsiflexion and eversion x 4-6 wk
  - physiotherapy: strengthening and proprioceptive retraining
- complete tear (Grade III)
  - below knee walking cast x 4-6 wk
  - physiotherapy: strengthening and proprioceptive retraining
  - surgical intervention may be required if chronic symptomatic instability develops

Foot

Talar Fracture

Mechanism
- axial loading or hyperdorsiflexion (MVC, fall from height)
- 60% of talus covered by articular cartilage
- talar neck is most common fracture of talus (50%)
- tenuous blood supply runs distal to proximal along talar neck
  - high risk of AVN with displaced fractures

Investigations
- x-rays: AP, lateral, Canale view
- CT to better characterize fracture
- MRI can clearly define extent of AVN

Treatment
- undisplaced: NWB below knee cast x 20-24 wk
- displaced: ORIF (high rate of nonunion, AVN)
- neck fracture: Pin (nondisplaced) or ORIF

Calcaneal Fracture

Mechanism
- high energy, axial loading: fall from height onto heels
- 10% of fractures associated with compression fractures of thoracic or lumbar spine (rule out spine injury)
- 75% intra-articular and 10% are bilateral

Physical Exam
- marked swelling, bruising on heel/sole
- wider, shortened, flatter heel when viewed from behind
- varus heel

Investigations
- x-rays: AP, lateral, oblique (Broden’s view)
- loss of Bohler’s angle
- CT: gold-standard, assess intra-articular extension

Treatment
- closed vs. open reduction is controversial
- NWB cast x 3 mo with early ROM and strengthening
**Achilles Tendonitis**

**Mechanism**
- chronic inflammation from activity or poor-fitting footwear
- may also develop heel bumps (retrocalcaneobursitis)

**Physical Exam**
- pain, stiffness, and crepitus with ROM
- thickened tendon, palpable bump

**Treatment**
- rest, NSAIDs, shoe wear modification
- heel sleeves and pads are mainstay of non-operative treatment
- gentle gastrocnemius-soleus stretching, eccentric training with physical therapy, deep tissue calf massage
- orthotics, open back shoes
- shockwave therapy in chronic tendonitis
- DO NOT inject steroids (risk of tendon rupture)

**Achilles Tendon Rupture**

**Mechanism**
- loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
- secondary to chronic tendonitis, steroid injection

**Clinical Features**
- audible pop, sudden pain with push off movement
- sensation of being kicked in heel when trying to plantar flex
- palpable gap
- apprehensive toe off when walking
- weak plantar flexion strength
- Thompson test: with patient prone, plantar flexion when calf is squeezed by examiner
  - no passive plantar flexion is positive test = ruptured tendon

**Treatment**
- low demand or elderly: cast foot in plantar flexion (to relax tendon) x 8-12 wk
- high demand: surgical repair, then cast as above x 6-8 wk

**Plantar Fasciitis (Heel Spur Syndrome)**

**Mechanism**
- repetitive strain injury causing microtears and inflammation of plantar fascia
- common in athletes (especially runners, dancers)
- also associated with obesity, DM, seronegative and seropositive arthritis

**Clinical Features**
- insidious onset of heel pain, pain when getting out of bed and stiffness
- intense pain when walking from rest that subsides as patient continues to walk, worse at end of day with prolonged standing
- swelling, tenderness over sole
- greatest at medial calcaneal tubercle and 1-2 cm distal along plantar fascia
- pain with toe dorsiflexion (stretches fascia)

**Investigations**
- plain radiographs to rule out fractures
- often see bony exostoses (heel spurs) at insertion of fascia into medial calcaneal tubercle
- spur is secondary to inflammation, not the cause of pain

**Treatment**
- pain control and stretching programs are first line
- rest, ice, NSAIDs, steroid injection
- physiotherapy: Achilles tendon and plantar fascia stretching, extracorporeal shockwave therapy
- orthotics with heel cup
  - to counteract pronation and disperse heel strike forces
- endoscopic surgical release of fascia in refractory cases
  - spur removal is not required
Bunions (Hallux Valgus)

Mechanism
• valgus alignment on 1st MTP (hallux valgus) causes eccentric pull of extensor and intrinsic muscles
• many associated deformities in foot from altered mechanics
• reactive exostosis forms with thickening of the skin creating a bunion
• most often associated with poor-fitting footwear (high heel and narrow toe box)
• can be hereditary (70% have family history)
• 10x more frequent in women

Clinical Features
• painful bursa over medial eminence of 1st MT head
• pronation (rotation inward) of great toe
• numbness over medial aspect of great toe

Investigations
• x-ray: standing AP/lateral/sesamoid view, NWB oblique

Treatment
• indications: painful corn or bunion, overriding 2nd toe
• non-operative first line
  • properly fitted shoes (low heel) and toe spacer
• surgical: goal is to restore normal anatomy, not cosmetic reasons alone
  • osteotomy with realignment of 1st MTP joint (Chevron Procedure)
  • arthrodesis

Metatarsal Fracture

• as with the hand, 1st, 4th, 5th MT are relatively mobile, while the 2nd and 3rd are fixed
• use Ottawa Foot Rules to determine need for x-ray

Table 23. Types of Metatarsal Fractures

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Mechanism</th>
<th>Clinical</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avulsion of Base of 5th MT</td>
<td>Sudden inversion followed by contraction of peroneus brevis</td>
<td>Tender base of 5th MT</td>
<td>Requires ORIF if displaced</td>
</tr>
<tr>
<td>Midshaft 5th MT (Jones Fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 5th MT</td>
<td>*NWB BK cast x 6 wk ORIF if athlete</td>
</tr>
<tr>
<td>Shaft 2nd, 3rd MT (March Fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 2nd or 3rd MT</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>1st MT</td>
<td>Trauma</td>
<td>Painful 1st MT</td>
<td>ORIF if displaced otherwise</td>
</tr>
<tr>
<td>*NWB BK = Non weight bearing, below knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tarso-MT Fracture – Dislocation (Lisfranc Fracture)</td>
<td>Fall onto plantar flexed foot or direct crush injury</td>
<td>Shortened forefoot prominent base</td>
<td>ORIF</td>
</tr>
</tbody>
</table>

Pediatric Orthopedics

Fractures in Children

• type of fracture
  • thicker, more active periosteum results in pediatric specific fractures: greenstick (one cortex), torus (i.e. ‘buckle’, impacted cortex) and plastic (bowing)
  • distal radius fracture most common in children (phalanges second), the majority are treated with closed reduction and casting
  • adults fracture through both cortices
  • epiphyseal growth plate
  • weaker part of bone, susceptible to fractures
  • plate often mistaken for fracture on x-ray and vice versa (x-ray opposite limb for comparison), especially in elbow
  • tensile strength of bone < ligaments in children, therefore clinician must be confident that fracture and/or growth plate injury have been ruled out before diagnosing a sprain
  • intra-articular fractures have worse consequences in children because they usually involve the growth plate
• anatomic reduction
  ▪ gold standard with adults
  ▪ may cause limb length discrepancy in children (overgrowth)
  ▪ accept greater angular deformity in children (remodeling minimizes deformity)
• time to heal
  ▪ shorter in children
  ▪ always be aware of the possibility of child abuse
  ▪ make sure stated mechanism compatible with injury
  ▪ high index of suspicion with fractures in non-ambulating children (<1 yr); look for other signs, including x-ray evidence of healing fractures at different sites and different stages of healing

**Stress Fractures**

**Mechanism**
• insufficiency fracture
  ▪ stress applied to a weak or structurally deficient bone
• fatigue fracture
  ▪ repetitive, excessive force applied to normal bone
• most common in adolescent athletes
• tibia is most common site

**Diagnosis and Treatment**
• localized pain and tenderness over the involved bone
• plain films may not show fracture for 2 wk
• bone scan positive in 12–15 d
• treatment is rest from strenuous activities to allow remodeling (can take several months)

**Evaluation of the Limping Child**

• see *Pediatrics*, P93

**Epiphyseal Injury**

Table 24. Salter-Harris Classification of Epiphyseal Injury

<table>
<thead>
<tr>
<th>SALT(E) Harris Type</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Straight through; Stable)</td>
<td>Transverse through growth plate</td>
<td>Closed reduction and cast immobilization (except SCFE – ORIF); heals well, 95% do not affect growth</td>
</tr>
<tr>
<td>II (Above)</td>
<td>Through metaphysis and along growth plate</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>III (Low)*</td>
<td>Through epiphysis to plate and along growth plate</td>
<td>Anatomic reduction by ORIF to prevent growth arrest, avoid fixation across growth plate</td>
</tr>
<tr>
<td>IV (Through and through)*</td>
<td>Through epiphysis and metaphysis</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>V (Ramp)*</td>
<td>Crush injury of growth plate</td>
<td>High incidence of growth arrest; no specific treatment</td>
</tr>
</tbody>
</table>

* Types III – IV are more likely to cause growth arrest and progressive deformity

**Slipped Capital Femoral Epiphysis**

• type I Salter-Harris epiphyseal injury at proximal hip
• most common adolescent hip disorder, peak incidence at pubertal growth spurt
• risk factors: male, obese (#1 factor), hypothyroid (risk of bilateral involvement)

**Etiology**
• multifactorial
  ▪ genetic: autosomal dominant, blacks > caucasians
  ▪ cartilaginous physis hypertrophies too rapidly under growth hormone effects
  ▪ sex hormone secretion, which stabilizes physis, has not yet begun
  ▪ overweight: mechanical stress
  ▪ trauma: causes acute slip

* In SCFE, bilateral involvement occurs in about 25%
Ages 10-14, below associated with hypothyroidism

Clinical Features
- acute: sudden, severe pain with limp
- chronic (typically): groin and anterior thigh pain, may present with knee pain
  - positive Trendelenburg sign on affected side, due to weakened gluteal muscles
- tender over joint capsule
- restricted internal rotation, abduction, flexion
- Whitman's sign: obligatory external rotation during passive flexion of hip
- clinical classification: stable vs. unstable (provides prognostic information)
  - unstable means patient cannot ambulate even with crutches

Investigations
- x-rays: AP, frog-leg, lateral radiographs both hips
  - posterior and medial slip
  - disruption of Klein’s line
  - AP view may be normal or show widened/lucent growth plate compared with opposite side

Treatment and Complications
- mild/moderate slip: stabilize physis with pins in current position
- severe slip: ORIF or pin physis without reduction and osteotomy after epiphyseal fusion
- complications: AVN (roughly half of unstable hips), chondrolysis (loss of articular cartilage, resulting in narrowing of joint space), pin penetration, premature OA, loss of ROM

Developmental Dysplasia of the Hip

- most common orthopedic disorder in newborns
- due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
- spectrum of conditions that lead to hip subluxation and dislocation
  - dislocated femoral head completely out of acetabulum
  - dislocatable head in socket
  - head subluxates out of joint when provoked
  - dysplastic acetabulum, more shallow and more vertical than normal
- painless (if painful suspect septic dislocation)

Physical Exam
- diagnosis is clinical
  - limited abduction of the flexed hip (<50-60°)
  - affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
  - Barlow’s test (for dislocatable hip)
    - flex hips and knees to 90° and grasp thigh
    - fully adduct hips, push posteriorly to try to dislocate hips
  - Ortolani’s test (for dislocated hip)
    - initial position as above but try to reduce hip with fingertips during abduction
    - positive test: palpable clunk is felt (not heard) if hip is reduced
  - Galeazzi’s sign
    - knees at unequal heights when hips and knees flexed
    - dislocated hip on side of lower knee
    - difficult test if child <1 yr
    - Trendelenburg test and gait useful if older (>2 yr)

Investigations
- U/S in first few months to view cartilage (bone is not calcified in newborns until 4-6 mo)
- follow up radiograph after 3 mo
- x-ray signs: false acetabulum, acetabular index >25°, broken Shenton’s line, femoral neck above Hilgenreiner’s line, ossification center outside of inner lower quadrant (quadrants formed by intersection of Hilgenreiner’s and Perkin’s line)

Treatment and Complications
- 0-6 mo: reduce hip using Pavlik harness to maintain abduction and flexion
- 6-18 mo: reduction under GA, hip spica cast x 2-3 mo (if Pavlik harness fails)
- >18 mo: open reduction; pelvic and/or femoral osteotomy
- complications
  - redislocation, inadequate reduction, stiffness
  - AVN of femoral head

5 Fs that Predispose to Developmental Dysplasia of the Hip
- Family history
- Female
- Frank breech
- First born
- Left hip
Legg-Calvé-Perthes Disease (Coxa Plana)

- idiopathic AVN of femoral head, presents at 4-8 yr of age
- etiology unknown, 12% bilateral, M:F = 5:1, 1/1,200
- associations
  - family history
  - low birth weight
  - abnormal pregnancy/delivery
  - ADHD in 33% of cases, delayed bone age in 89%
- key features
  - AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodelling of regenerated bone

Clinical Features
- child with antalgic limp ± pain
- intermittent knee, hip, groin, or thigh pain
- flexion contracture (stiff hip): decreased internal rotation and abduction of hip

Investigations
- x-rays: AP pelvis, frog leg laterals
  - may be negative early (if high index of suspicion, move to bone scan or MRI)
  - eventually, characteristic collapse of femoral head (diagnostic)

Treatment
- goal is to preserve ROM and keep femoral head contained in acetabulum
- physiotherapy: ROM exercises
- brace in flexion and abduction x 2-3 yr (controversial)
- femoral or pelvic osteotomy (>8 yr of age or severe)
  - prognosis better in males, <5 yr, <50% of femoral head involved, abduction >30°
- 60% of involved hips do not require operative intervention
- Natural history is early onset OA and decreased ROM

Osgood-Schlatter Disease

Mechanism
- repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)

Clinical Features
- tender lump over tibial tuberosity
- pain on resisted leg extension
- anterior knee pain exacerbated by jumping or kneeling, relieved by rest

Investigations
- x-rays: lateral knee: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

Treatment
- benign, self-limited condition, does not resolve until growth halts
- may restrict activities such as basketball or cycling
- NSIADS, rest, flexibility, isometric strengthening exercises

Congenital Talipes Equinovarus (Club Foot)

Etiology
- intrinsic causes (neurologic, muscular, or connective tissue diseases) vs. extrinsic (intrauterine growth restriction), may be idiopathic, neurogenic, or syndrome-associated
- fixed deformity
- 3 parts to deformity
  - talipes: talus is inverted and internally rotated
  - equinus: ankle is plantar flexed
  - varus: heel and forefoot are in varus (supinated)
- 1-2/1,000 newborns, 50% bilateral, occurrence M:F, severity F>M

Physical Exam
- examine hips for associated DDH
- examine knees for deformity
- examine back for dysraphism (unfused vertebral bodies)
Treatment
- correct deformities in the following order (Ponseti Technique; 90% success rate)
  - forefoot adduction, ankle inversion, equinus
  - change strapping/cast q1-2wk
  - surgical release in refractory case (rare)
  - delayed until 3-4 mo of age
- 3 yr recurrence rate = 5-10%
- mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf muscle atrophy

Scoliosis

Definition
- lateral curvature of spine with vertebral rotation

Epidemiology
- age: 10-14 yr
- more frequent and more severe in females

Etiology
- idiopathic: most common (90%)
- congenital: vertebrae fail to form or segment
- neuromuscular: UMN or LMN lesion, myopathy
- postural: leg length discrepancy, muscle spasm
- other: osteochondrodystrophies, neoplastic, traumatic

Clinical Features
- ± back pain
- 1° curve where several vertebrae affected
- 2° curves above and below fixed 1° curve to try and maintain normal position of head and pelvis
- asymmetric shoulder height when bent forward
- Adam's test: rib hump when bent forward
- prominent scapulae, creased flank, asymmetric pelvis
- associated posterior midline skin lesions in neuromuscular scolioses
  - café-au-lait spots, dimples, neurofibromas
- axillary freckling, hemangiomas, hair patches
- associated pes cavus or leg atrophy
- apparent leg length discrepancy

X-Rays
- 3-foot standing, AP, lateral
  - measure curvature: Cobb angle
  - may have associated kyphosis

Treatment
- based on Cobb angle
  - <25°: observe for changes with serial radiographs
  - >25° or progressive: bracing (many types) that halt/slow curve progression but do NOT reverse deformity
  - >45°, cosmetically unacceptable or respiratory problems: surgical correction (spinal fusion)

Bone Tumors
- primary bone tumors are rare after 3rd decade
- metastases to bone are relatively common after 3rd decade

Table 25. Distinguishing Benign from Malignant Bone Lesions on X-ray

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No periosteal reaction</td>
<td>Acute periosteal reaction</td>
</tr>
<tr>
<td>Thick endosteal reaction</td>
<td>• Codman’s triangle</td>
</tr>
<tr>
<td>Well developed bone formation</td>
<td>• “Onion skin”</td>
</tr>
<tr>
<td>Intracortical and even calcification</td>
<td>• “Sunburst”</td>
</tr>
<tr>
<td>Broad border between lesion and normal bone</td>
<td>Varied bone formation</td>
</tr>
<tr>
<td>Extraosseous and irregular calcification</td>
<td>Extraosseous and irregular calcification</td>
</tr>
</tbody>
</table>

Adapted from: Buckholtz RW, Heckman JD. Rockwood and Green's Fractures in Adults. Volume 1. Philadelphia: Lippincott Williams & Wilkins, 2001; 558
Diagnosis
- pain, swelling, tenderness, rarely regional adenopathy
- routine x-ray findings
  - location (which bone, diaphysis, metaphysis, epiphysis)
  - size
  - lytic/lucent vs. sclerotic
  - involvement (cortex, medulla, soft tissue)
  - matrix (radiolucent, radiodense or calcified)
  - periosteal reaction
  - margin (geographic vs. permeative)
  - any pathological fracture
  - soft tissue swelling
- malignancy is suggested by rapid growth, warmth, tenderness, lack of sharp definition
- staging should include
  - blood work including liver enzymes
  - CT chest
  - bone scan
  - bone biopsy
    - should be referred to specialized center prior to biopsy
    - classified into benign, benign aggressive, and malignant
  - MRI of affected bone

Benign Active Bone Tumors

Bone-Forming Tumors

Osteoid Osteoma
- peak incidence in 2nd and 3rd decades, M:F = 2:1 (young males)
- proximal femur and tibia diaphysis most common locations
- not known to metastasize
- radiographic findings: small, round radiolucent nidus (<1 cm) surrounded by dense sclerotic bone (“bull’s-eye”)
- symptoms: produces severe intermittent pain from prostaglandin secretion and COX1/2 expression, mostly at night (diurnal prostaglandin production), thus is characteristically relieved by NSAIDs
- treatment: NSAIDs for night pain; surgical resection of nidus

Fibrous Lesions

Fibrous Cortical Defect
- occur in as many as 35% of children, peak incidence between 2-20 yr old, higher prevalence in males
- femur and proximal tibia most common locations, 50% of patients have multiple defects usually bilateral, symmetrical
- radiographic findings: diagnostic, metaphyseal eccentric ‘bubbly’ lytic lesion near physis; thin smooth/lobulated well-defined sclerotic margin
- treatment: most lesions resolve spontaneously

Osteochondroma
- 2nd and 3rd decades, M:F = 1.8:1
- most common of all benign bone tumors – 45%
- metaphysis of long bone near tendon attachment sites (usually distal femur, proximal tibia, or proximal humerus)
  - radiographic findings: cartilage-capped bony spur on surface of bone (‘mushroom’ on x-ray)
  - may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
  - generally very slow growing and asymptomatic unless impinging on neurovascular structure (‘painless mass’)
  - growth usually ceases when skeletal maturity is reached
  - malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)

Enchondroma
- 2nd and 3rd decades
- 60% occur in the small tubular bones of the hand and foot; others in femur (20%), humerus, ribs
- benign cartilagenous growth, an abnormality of chondroblasts, develops in medullary cavity
  - single/multiple enlarged rarefied areas in tubular bones
  - lytic lesion with sharp margination and central calcification
• malignant degeneration to chondrosarcoma occurs in 1-2% (pain in absence of pathologic fracture is an important clue)
• not known to metastasize

CYSTIC LESIONS

Unicameral/Solitary Bone Cyst
• most common cystic lesion
• children and young adults, peak incidence during first 2 decades, M:F = 2:1
• proximal humerus and femur most common
• symptoms: asymptomatic, or local pain; complete pathological fracture (50% presentations) or incidental detection
• radiographic findings: lytic translucent area on metaphyseal side of growth plate, cortex thinned/expanded; well defined lesion
• treatment: aspiration followed by steroid injection; curettage ± bone graft indicated if re-fracture likely

Benign Aggressive Bone Tumors

Giant Cell Tumors/Aneurysmal Bone Cyst/Osteoblastoma
• affects patients of skeletal maturity, peak 3rd decade
• osteoblastoma: found in the distal femur, proximal tibia, distal radius, sacrum, tarsal bones, spine
• giant cell tumor: pulmonary metastases in 3%
• aneurysmal bone cysts: either solid with fibrous/granular tissue, or blood-filled
• radiographic findings
  • giant cell tumor: eccentric lytic lesions, in epiphyses adjacent to subchondral bone; may break through cortex; T2 MRI enhances fluid within lesion (hyper-intense signal)
  • aneurysmal bone cyst: expanded with honeycomb shape
  • osteoblastoma: often nonspecific; calcified central nidus (>2 cm) with radiolucent halo and sclerosis
• symptoms: local tenderness and swelling, pain may be progressive (giant cell tumors), ± symptoms of nerve root compression (osteoblastoma)
• 15% recur within 2 yr of surgery

Treatment
• intralesional curettage + bone graft or cement
• wide local excision of expendable bones

Malignant Bone Tumors

Table 26. Most Common Malignant Tumor Types for Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>1-10</td>
<td>Ewing’s of tubular bones</td>
</tr>
<tr>
<td>10-30</td>
<td>Osteosarcoma, Ewing’s of flat bones</td>
</tr>
<tr>
<td>30-40</td>
<td>Reticulum cell sarcoma, fibrosarcoma, periosteal osteosarcoma, malignant giant cell tumor, lymphoma</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Metastatic carcinoma, multiple myeloma, chondrosarcoma</td>
</tr>
</tbody>
</table>

Osteosarcoma
• most frequently diagnosed in 2nd decade of life (60%), 2nd most common primary malignancy in adults
• history of Paget’s disease (elderly patients), previous radiation treatment
• predilection for sites of rapid growth: distal femur (45%), proximal tibia (20%), and proximal humerus (15%)
  • invasive, variable histology; frequent metastases without treatment (lung most common)
• painful symptoms: progressive pain, night pain, poorly defined swelling, decreased ROM
• radiographic findings:
  • characteristic periosteal reaction: Codman’s triangle (see Figure 56) or “sunburst” spicule formation (tumor extension into periosteum)
  • destructive lesion in metaphysis may cross epiphyseal plate
• management: complete resection (limb salvage, rarely amputation), neo-adjuvant chemo; bone scan – rule out skeletal metastases, CT chest – rule out pulmonary metastases
• prognosis: 70% (high-grade); 90% (low-grade)
Chondrosarcoma (see Figure 60)
- primary (2/3 cases)
  - patient >40 yr; previous normal bone expands into cortex to give pain, pathological fracture, flecks of calcification
- secondary (1/3 cases)
  - malignant degeneration of pre-existing cartilage tumor such as enchondroma or osteochondroma
  - younger age group and better prognosis than primary chondrosarcoma
- symptoms: progressive pain, uncommonly palpable mass
- radiographic findings: in medullary cavity, irregular “popcorn” calcification
- treatment: unresponsive to chemotherapy, treat with aggressive surgical resection + reconstruction; regular follow-up x-rays of resection site and chest
- prognosis: 10 yr survival 90% low-grade, 20-40% high-grade

Ewing’s Sarcoma
- most occur between 5-25 yr old
- florid periosteal reaction in metaphyses of long bone with diaphyseal extension
- metastases frequent without treatment
- signs/symptoms: presents with pain, mild fever, erythema and swelling, anemia, increased WBC, ESR, LDH (mimics an infection)
- radiographic findings: moth-eaten appearance with periosteal lamellated pattern (“onion-skinning”)
- treatment: resection, chemotherapy, radiation
- prognosis – 70%, worst prognostic factor is distant metastases

Multiple Myeloma
- most common primary malignant tumor of bone in adults (~43%)
- 90% occur in people >40 yr old, M:F = 2:1, African-Americans (twice as common)
- signs/symptoms: bone pain (cardinal early symptom), compression/pathological fractures, renal failure, nephritis, high incidence of infections (e.g. pyelonephritis/pneumonia), systemic (weakness, weight loss, anorexia)
- labs: anemia, thrombocytopenia, increased ESR, hypercalcemia
- radiographic findings: multiple, “punched-out” well-demarcated lesions, no surrounding sclerosis, marked bone expansion
- diagnosis
  - serum/urine immunoelectrophoresis (monoclonal gammopathy)
  - CT-guided biopsy of lytic lesions at multiple bony sites
- treatment: chemotherapy, bisphosphonates, radiation, surgery for symptomatic lesions or impending fractures – debulking, internal fixation
- prognosis: most 3 yr after diagnosis
- see Hematology: H49

Bone Metastases
- 2/3 from breast or prostate; also consider thyroid, lung, kidney
- usually osteolytic; prostate occasionally osteoblastic
- bone scan for MSK involvement, MRI for spinal involvement may be helpful
- stabilization of impending fractures
  - internal fixation, IM rods
  - bone cement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Upper arm, Lower extremity, Peritrochanteric</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild, Moderate, Severe</td>
</tr>
<tr>
<td>Lesion</td>
<td>Blastic, Mixed, Lytic</td>
</tr>
<tr>
<td>Size</td>
<td>&lt; 1/3 bone diameter, 1/3-2/3 diameter, &gt; 2/3 diameter</td>
</tr>
</tbody>
</table>

Table 27. Mirel’s Criteria for Impending Fracture Risk and Prophylactic Internal Fixation
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefazolin (Ancef®)</td>
<td>1-2 g IV q8h</td>
<td>Prophylactically before orthopedic surgery</td>
<td>First generation cephalosporin; do not use with penicillin allergy</td>
</tr>
<tr>
<td>heparin</td>
<td>5000 IU SC q12h</td>
<td>To prevent venous thrombosis and pulmonary emboli</td>
<td>Monitor platelets, follow PTT which should rise 1.5-2x</td>
</tr>
<tr>
<td>LMWH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dalteparin (Fragmin®)</td>
<td>5000 IU SC OD</td>
<td>DVT prophylaxis especially in hip and knee surgery</td>
<td>Fixed dose, no monitoring, improved bioavailability, increased bleeding rates</td>
</tr>
<tr>
<td>enoxaparin (Lovenox®)</td>
<td>30-40 mg SC bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fondaparinux (Arixtra®)</td>
<td>2.5 mg SC OD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>midazolam (Versed®)</td>
<td>0.02-0.04 mg/kg IV</td>
<td>Conscious sedation for short procedures</td>
<td>Medication used during fracture reduction – monitor for respiratory depression</td>
</tr>
<tr>
<td>fentanyl (Sublimaze®)</td>
<td>0.5-3 µg/kg IV</td>
<td>Conscious sedation for short procedures</td>
<td>Short acting anesthetic used in conjunction with midazolam (Versed®)</td>
</tr>
<tr>
<td>triamcinolone (Aristocort®) – an injectable steroid</td>
<td>0.5-1 mL of 25 mg/mL Suspension (injected into inflamed joint or bursa); amount varies by joint size</td>
<td>Potent anti-inflammatory effect; increased pain for 24 h, rarely causes fat necrosis and skin depigmentation</td>
<td></td>
</tr>
<tr>
<td>naproxen (Aleve®, Naprosyn®)</td>
<td>250-500 mg bid</td>
<td>Pain due to inflammation, arthritis, soft tissue injury</td>
<td>NSAID, may cause gastric erosion and bleeding</td>
</tr>
<tr>
<td>misoprostol (Cytotec®)</td>
<td>200 µg qid</td>
<td>Prophylaxis of HO after THA</td>
<td>Use with indomethacin</td>
</tr>
<tr>
<td>indomethacin (Indocid®)</td>
<td>25 mg PO tid</td>
<td>Prophylaxis of HO after THA</td>
<td>Use with misoprostol</td>
</tr>
<tr>
<td>ibuprofen (Advil®, Motrin®)</td>
<td>200-400 mg tid</td>
<td>Pain (including post-operative), inflammation (including arthritis)</td>
<td>NSAID, may cause gastric erosion and bleeding</td>
</tr>
<tr>
<td>propofol (Diprivan®)</td>
<td>1-2 mg/kg IV maintenance 0.5 mg/kg</td>
<td>Conscious sedation for short procedures</td>
<td>Short acting anesthetic often used in conjunction with fentanyl (Sublimaze®)</td>
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<th>Definition</th>
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<td>ABR</td>
<td>auditory brainstem response</td>
</tr>
<tr>
<td>AC</td>
<td>air conduction</td>
</tr>
<tr>
<td>AGM</td>
<td>acute otitis media</td>
</tr>
<tr>
<td>BAH A</td>
<td>bone anchored hearing aid</td>
</tr>
<tr>
<td>BG</td>
<td>bone conduction</td>
</tr>
<tr>
<td>CHL</td>
<td>conductive hearing loss</td>
</tr>
<tr>
<td>CPA</td>
<td>cerebellar angle</td>
</tr>
<tr>
<td>EAC</td>
<td>external auditory canal</td>
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<td>EBV</td>
<td>Epstein-Barr virus</td>
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<td>FAP</td>
<td>familial adenomatous polyposis</td>
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<td>FESS</td>
<td>functional endoscopic sinus surgery</td>
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<td>fine needle aspiration</td>
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<td>gastroesophageal reflux disease</td>
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<td>granulomatosis with polyangiitis</td>
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<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>SMHL</td>
<td>semicircular canal</td>
</tr>
<tr>
<td>SRT</td>
<td>speech reception threshold</td>
</tr>
<tr>
<td>TEF</td>
<td>tracheoesophageal fistula</td>
</tr>
<tr>
<td>TM</td>
<td>tympanic membrane</td>
</tr>
<tr>
<td>TNM</td>
<td>tumor, node, metastases</td>
</tr>
<tr>
<td>URI T</td>
<td>upper respiratory tract infection</td>
</tr>
</tbody>
</table>

**Basic Anatomy Review**

**Ear**

![Surface anatomy of the external ear; anatomy of ear](image1)

- **External**: Temporalis fascia and muscle
- **Middle**: Malleus, Incus, Stapes
- **Inner**: Semicircular canals

![Normal appearance of right tympanic membrane on otoscopy](image2)

- **Tympanic membrane viewed through speculum**
  - Pars flaccida
  - Neck of malleus
  - Lateral process of malleus
  - Incus long process
  - Stapes
  - Tensor of stapedius muscle
  - Long process of malleus
  - Umpio (Flat portion)
  - Fossa of round (cochlear) window
  - Cone of light

- **View into tympanic cavity after removal of tympanic membrane**
  - Tensor tympani tendon
  - Tensor tympani muscle
  - Tympanic plexus (branch of CN IX)
  - Hypotympanum
  - Annulus

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Nose

Figure 3. Nasal anatomy

Figure 4. Nasal septum and its arterial supply (see Epistaxis, OT27 for detailed blood supply)

Figure 5. Anatomy of the four paranasal sinuses: maxillary, ethmoid, sphenoid, and frontal

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Drainage into Nasal Cavity
- Superior meatus: sphenoid (via sphenoethmoidal recess), posterior ethmoid sinuses
- Middle meatus: frontal, maxillary, anterior ethmoid sinuses
- Inferior meatus: nasolacrimal duct

Throat

Figure 6. Anatomy of a normal larynx; superior view of larynx on indirect laryngoscopy
Head and Neck

**Figure 7. Extratemporal segment of facial nerve**
Branches of facial nerve (in order from superior to inferior)

To Zanzibar By Motor Car

**Figure 8. Blood supply to the face**
Branches of the external carotid artery (in order from inferior to superior)

Some Angry Lady Figured Out PMS

**Figure 9. Anatomy of the neck**
Anatomical Triangles of the Neck

Anterior triangle:
- bounded by anterior border of SCM, midline of neck, and lower border of mandible
- divided into
  - submental triangle: bounded by both anterior bellies of digastric and hyoid bone
  - digastric triangle: bounded by anterior and posterior bellies of digastric, and inferior border of mandible
  - carotid triangle: bounded by sternocleidomastoid, anterior belly of omohyoid, and posterior belly of digastric
    - contains: tail of parotid, submandibular gland, hypoglossal nerve, carotid bifurcation, and lymph nodes

Posterior triangle
- bounded by posterior border of sternocleidomastoid, anterior border of trapezius, and middle third of clavicle
- divided into
  - occipital triangle: superior to posterior belly of the omohyoid
  - subclavian triangle: inferior to posterior belly of omohyoid
- contains: spinal accessory nerve and lymph nodes

Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of Neck

<table>
<thead>
<tr>
<th>Nodal Group/Level</th>
<th>Location</th>
<th>Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suboccipital (S)</td>
<td>Base of skull, posterior</td>
<td>Posterior scalp</td>
</tr>
<tr>
<td>2. Retroauricular (R)</td>
<td>Superficial to mastoid process</td>
<td>Scalp, temporal region, external auditory meatus, posterior pinna</td>
</tr>
<tr>
<td>3. Parotid-preauricular (P)</td>
<td>Anterior to ear</td>
<td>External auditory meatus, anterior pinna, soft tissue of frontal and temporal regions, root of nose, eyelids, palpebral conjunctiva</td>
</tr>
<tr>
<td>4. Submental (Level IA)</td>
<td>(Midline) Anterior bellies of digastric muscles, tip of mandible, and hyoid bone</td>
<td>Floor of mouth, anterior tongue, anterior mandibular alveolar ridge, lower lip</td>
</tr>
<tr>
<td>5. Submandibular (Level IB)</td>
<td>Anterior belly of digastric muscle, stylohyoid muscle, body of mandible</td>
<td>Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland</td>
</tr>
<tr>
<td>6. Upper jugular (Levels IIA and IIB)</td>
<td>Skull base to inferior border of hyoid bone along SCM muscle</td>
<td>Oral cavity, nasal cavity, naso/oro/hypopharynx, larynx, parotid glands</td>
</tr>
<tr>
<td>7. Middle jugular (Level III)</td>
<td>Inferior border of hyoid bone to inferior border of cricoid cartilage along SCM muscle</td>
<td>Oral cavity, naso/oro/hypopharynx, larynx</td>
</tr>
<tr>
<td>8. Lower jugular* (Level IV)</td>
<td>Inferior border of cricoid cartilage to clavicle along SCM muscle</td>
<td>Hypopharynx, thyroid, cervical esophagus, larynx</td>
</tr>
<tr>
<td>9. Posterior triangle** (Levels VA and VB)</td>
<td>Posterior border of SCM, anterior border of trapezius, from skull base to clavicle</td>
<td>Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck</td>
</tr>
<tr>
<td>10. Anterior compartment*** (Level VI)</td>
<td>(Midline) Hyoid bone to suprasternal notch between the common carotid arteries</td>
<td>Thyroid gland, glottic and subglottic larynx, apex of piriform sinus, cervical esophagus</td>
</tr>
</tbody>
</table>

*Virchow node: left lower jugular (level IV) supraclavicular node
**Includes some supraclavicular nodes
***Includes pretracheal, pretracheal, paratracheal, and parathyroidal nodes

Function of Facial Nerve
“Ears, Tears, Face, Taste”
Ears: stapedius muscle
Tears: lacrimation (lacrimal gland) and salivation (parotid)
Face: muscles of facial expression
Taste: sensory anterior 2/3 of tongue (via chorda tympani)

4 Strap Muscles of the Neck
- Thyrohyoid
- Omohyoid
- Sternohyoid
- Sternothyroid
### Differential Diagnoses of Common Presenting Problems

#### Dizziness

- **Peripheral (Vestibular)**
  - Benign paroxysmal positional vertigo (BPPV)
  - Labyrinthitis
  - Vestibular neuronitis
  - Meniere’s disease
  - Autoimmune inner ear disease
  - Cholesteatoma
  - Ototoxic drug exposure
  - Perilymph fistula
  - Recurrent vestibulopathy
  - Superior semicircular canal dehiscence
  - Temporal bone fracture

- **Central**
  - Cerebrovascular disorders
    - Cerebellar infarction
    - Transient ischemic attacks
    - Vertebrobasilar insufficiency
    - Wallenberg’s syndrome
  - Multiple sclerosis
  - Inflammation
    - Cerebellar abscess
    - Meningitis
  - Toxic: alcohol, hypnotics, drugs
  - Trauma: cerebellar contusion
  - Tumours
    - CPA tumors
    - Glomus tumors
    - Posterior fossa tumors

- **Organic Diseases**
  - Anemia
  - Cardiac
    - Aortic stenosis
    - Arrhythmias
    - Orthostatic hypotension
  - Trauma
    - Cervical arthritis
    - Thyroiditis
  - Other
    - Glossopharyngeal neuralgia
    - Neoplasm of oral cavity, larynx, pharynx
    - Teeth

- **Functional**
  - Anxiety
    - Depression
    - Panic disorder (hyperventilation)
    - Personality disorder
    - Phobic dizziness

**5 “D”s of Vertebrobasilar Insufficiency**
- Drop attacks
- Diplopia
- Dysarthria
- Dizziness
- Dysphagia

True nystagmus and vertigo caused by a peripheral lesion will never last longer than a couple of weeks because of compensation. Central lesions do not compensate, hence nystagmus and vertigo will persist.

**Common causes in bold**

#### Otalgia

- **External Ear**
  - Infection
    - Auricular cellulitis
    - External canal abscess
    - Herpes simplex/zoster
    - Otitis externa
  - Trauma
    - Burns
    - Frostbite
    - Hematoma
    - Lacerations
  - Other
    - Cerumen impaction
    - Foreign body
    - Neoplasm of external canal

- **Middle/Inner Ear**
  - Infection
    - ADOM
    - Mastoiditis
    - Myringitis
    - Otitis media with effusion
    - Skull base infections
    - Trauma
    - Barotrauma
    - Traumatic perforation
    - Other
      - Cholesteatoma
      - Neoplasm
      - Wegener’s granulomatosis

- **Referred Pain**
  - Infection
    - Ramsay Hunt syndrome
    - Tonsillitis
    - Tracheitis
    - Trauma
    - Cervical arthritis
    - Thyroiditis
  - Other
    - Glossopharyngeal neuralgia
    - Neoplasm of oral cavity, larynx, pharynx
    - Teeth
    - TMJ syndrome
    - Trismus

Figure 11. Differential diagnosis of dizziness

Figure 12. Differential diagnosis of otalgia
Hearing Loss

**Conductive**
- Impacted cerumen
- Otitis externa
- Foreign body
- Keratosis aburatorum
- Exostoses, osteomas
- Tumor of canal
- Congenital stenosis/microtia

**Middle Ear**
- AOM
- Otitis media with effusion
- TM perforation
- Otosclerosis
- Tympanosclerosis
- Eustachian tube dysfunction
- Cholesteatoma
- Otosclerotic malformations
- Osicular disconnection
- Hemotympanum
- Stapedius muscle spasm
- Middle ear tumor

**Sensorineural**
- Genetic
- Non-syndrome associated
- Syndrome associated
  - Intrauterine infections (i.e., TORCH)
  - Teratogens
  - Perinatal hypoxia
  - Prematurity/low birth weight
  - Hyperbilirubinemia

**Presbycusis**
- Noise-induced
- Menière’s disease
- Labyrinthitis
- Sudden SNHL
- Autoimmune inner ear disease
- Ototoxic drug exposure
- Temporal bone trauma
- Infectious
  - Postmeningitis
  - Syphilis
  - Tuberculosis
  - CMV, HSV
- Neoplastic
  - Acoustic neuroma
  - CPA tumors
  - Vascular occlusion/emboli
  - Auditory neuropathy

Common causes in bold

Figure 13. Differential diagnosis of hearing loss

Tinnitus

**Subjective**
- Only heard by patient
  - (common)

**Objective**
- Can be heard by others
  - (rare)

**Otolagic**
- Presbycusis
- Noise-induced hearing loss
- Otitis media with effusion
- Menière’s disease
- Otosclerosis
- Cerumen
- Foreign body against TM

**Drugs**
- NSAIDs
- Aminoglycosides
- Antihypertensives
- Heavy metals

**Metabolic**
- Hyper/hypothyroidism
- Hyperlipidemia
- Vitamin A, B, Zinc deficiency

**Neurologic**
- Head trauma
- Multiple sclerosis
- CPA tumors
- Psychiatric
- Anxiety
- Depression

**Vascular**
- Benign intracranial hypertension
- Arteriovenous malformation
- Glomus tympanicum
- Glomus jugulare
- Arterial bruits:
  - High-riding carotid artery
  - Vascular loop
  - Persistent stapedial artery
- Carotid stenosis

Venous hum:
- High jugular bulb
- Hypertension
- Hyper/hypothyroidism

**Mechanical**
- Patulous eustachian tube
- Palatal myoclonus
- Stapedius muscle spasm

Common causes in bold

Figure 14. Differential diagnosis of tinnitus

Glomus Tympanicum/Jugulare Tumor Signs and Symptoms
- Pulsatile tinnitus
- Hearing loss
- Blue mass behind TM
- Brown’s sign (blanching of the TM with pneumatic otoscopy)

Tinnitus is most commonly associated with SNHL
# Nasal Obstruction

## Table 2. Differential Diagnosis of Nasal Obstruction

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nasal Cavity</strong></td>
<td><strong>Nasal Cavity</strong></td>
</tr>
<tr>
<td>• Rhinitis</td>
<td>• Nasal dermoid cyst</td>
</tr>
<tr>
<td>• Acute/chronic</td>
<td>• Encephalocele</td>
</tr>
<tr>
<td>• Vasomotor</td>
<td>• Gloma</td>
</tr>
<tr>
<td>• Allergic</td>
<td>• Choanal atresia</td>
</tr>
<tr>
<td>• Rhinosinusitis</td>
<td></td>
</tr>
<tr>
<td>• Foreign bodies</td>
<td></td>
</tr>
<tr>
<td>• Enlarged turbinates</td>
<td></td>
</tr>
<tr>
<td>• Tumor</td>
<td></td>
</tr>
<tr>
<td>• Benign: polyps, inverting papilloma</td>
<td></td>
</tr>
<tr>
<td>• Malignant</td>
<td></td>
</tr>
<tr>
<td>• SCC</td>
<td></td>
</tr>
<tr>
<td>• Esthesioneuroblastoma (olfactory neuroblastoma)</td>
<td></td>
</tr>
<tr>
<td>• Adenocarcinoma</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nasal Septum</th>
<th>Nasal Septum</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Septal deviation</td>
<td>• Septal deviation</td>
</tr>
<tr>
<td>• Septal hematoma/abscess</td>
<td>• Septal hematoma/abscess</td>
</tr>
<tr>
<td>• Dislocated septum</td>
<td>• Dislocated septum</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nasopharynx</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Adenoid hypertrophy</td>
<td></td>
</tr>
<tr>
<td>• Tumor</td>
<td></td>
</tr>
<tr>
<td>• Benign: juvenile nasopharyngeal angiofibroma (JNA), polyps</td>
<td></td>
</tr>
<tr>
<td>• Malignant: nasopharyngeal carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systemic</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Granulomatous diseases, diabetes, vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

## Hoarseness

### Table 3. Differential Diagnosis of Hoarseness

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Inflammatory</th>
<th>Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute/chronic laryngitis</td>
<td>• GERD</td>
<td>• External laryngeal trauma</td>
</tr>
<tr>
<td>• Laryngotracheobronchitis (croup)</td>
<td>• Vocal cord polyps/nodules</td>
<td>• Endoscopy and endotracheal tube (e.g. intubation granuloma)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neoplasia</th>
<th>Cysts</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Benign tumor</td>
<td>• Retention cysts</td>
<td>• Endocrine</td>
</tr>
<tr>
<td>• Papillomas (HPV infection)</td>
<td></td>
<td>• Hypothyroidism</td>
</tr>
<tr>
<td>• Minor salivary gland tumors</td>
<td></td>
<td>• Virilization</td>
</tr>
<tr>
<td>• Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Connective tissue disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• SLE</td>
</tr>
</tbody>
</table>

### Neurologic

(vocal cord paralysis due to superior ± recurrent laryngeal nerve injury)

<table>
<thead>
<tr>
<th>Central lesions</th>
<th>Lateral lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cerebrovascular accident (CVA)</td>
<td>• Unilateral</td>
</tr>
<tr>
<td>• Head injury</td>
<td>• Lung malignancy</td>
</tr>
<tr>
<td>• Multiple sclerosis (MS)</td>
<td></td>
</tr>
<tr>
<td>• Skull base tumors</td>
<td></td>
</tr>
<tr>
<td>• Arnold-Chiari malformation</td>
<td></td>
</tr>
<tr>
<td>• Peripheral lesions</td>
<td></td>
</tr>
<tr>
<td>• Unilateral</td>
<td></td>
</tr>
<tr>
<td>• Lung malignancy</td>
<td></td>
</tr>
</tbody>
</table>

### Functional

| Psychogenic aphonya (hysterical aphonya) | |

### Congenital

<table>
<thead>
<tr>
<th>Laryngomalacia</th>
<th>Laryngeal web</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laryngeal atresia</td>
<td></td>
</tr>
</tbody>
</table>
Neck Mass

Figure 15. Differential diagnosis of a neck mass

Hearing

Normal Hearing Physiology

- **Conductive pathway (external auditory canal to cochlea):** air conduction of sound energy down the EAC → vibration of the tympanic membrane (area effect) → sequential vibration of the middle ear ossicles: malleus, incus, stapes (lever effect) → transmission of amplified vibrations from the stapes footplate in the middle ear to the oval window of the cochlea in the inner ear → pressure differential on cochlear fluid creates movement along the basilar membrane within the cochlea from base to apex
- **Neural pathway (nerve to brain):** basilar membrane vibration stimulates overlying hair cells in the organ of Corti → stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII → cochlear nucleus → superior olivary nucleus → lateral lemniscus → inferior colliculus → Sylvian fissure of temporal lobe

Types of Hearing Loss

1. **Conductive Hearing Loss**
   - conduction of sound to the cochlea is impaired
   - can be caused by external and middle ear disease

2. **Sensorineural Hearing Loss**
   - due to a defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
   - can be caused by disease of the inner ear (cochlea), acoustic nerve (CN VIII), brainstem, or cortex

3. **Mixed Hearing Loss**
   - combination of conductive and sensorineural hearing loss

Auditory Acuity

- whispered-voice test: mask one ear and whisper into the other
- tuning fork tests (see Table 4; audiogram is of greater utility)
- sensitivity depends on which tuning fork used (256 Hz, 512 Hz, 1024 Hz; 512 Hz has greatest sensitivity)
  - **Rinne test**
    - 512 Hz tuning fork is struck and held firmly on mastoid process to test BC; the tuning fork is then placed beside the pinna to test AC
    - if AC > BC → positive Rinne (normal)
  - **Weber test**
    - 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative) or is lateralized to one side (Weber right, Weber left)
    - can place vibrating fork on patient’s chin while they clench their teeth, or directly on teeth to elicit more reliable response
    - will only lateralize if difference in hearing loss between ears is >6 dB

Order of the Neural Pathway (with Corresponding Waves on ABR)

<table>
<thead>
<tr>
<th>E CO LI</th>
<th>Eighth cranial nerve (I – II)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Olivary nucleus</td>
<td></td>
</tr>
<tr>
<td>Lateral lemniscus (IV – V)</td>
<td></td>
</tr>
<tr>
<td>Inferior colliculus</td>
<td></td>
</tr>
</tbody>
</table>

Weber Test Lateralization = ipsilateral conductive hearing loss or contralateral sensorineural hearing loss

The Weber test is more sensitive in detecting conductive hearing loss than the Rinne test

**HL** = Intensity x Duration
Table 4. The Interpretation of Tuning Fork Tests

<table>
<thead>
<tr>
<th>Examples</th>
<th>Weber</th>
<th>Rinne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or bilateral sensorineural hearing loss</td>
<td>Central</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided conductive hearing loss, normal left ear</td>
<td>Lateralizes to right</td>
<td>BC &gt; AC (−) right</td>
</tr>
<tr>
<td>Right-sided sensorineural hearing loss, normal left ear</td>
<td>Lateralizes to left</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided severe sensorineural hearing loss or dead right ear, normal left ear</td>
<td>Lateralizes to left</td>
<td>BC &gt; AC (−) right*</td>
</tr>
</tbody>
</table>

*A vibrating tuning fork on the mastoid stimulates the cochlea bilaterally, therefore in this case the left cochlea is stimulated by the Rinne test on the right (e.g. a false negative test). These tests are not valid if the ear canals are obstructed with cerumen (e.g. will create conductive loss).

Pure Tone Audiometry

- A threshold is the lowest intensity level at which a patient can hear the tone 50% of the time
- Thresholds are obtained for each ear at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz
- Air conduction thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function
- Bone conduction thresholds are obtained with bone conduction oscillators which bypass the outer and middle ear

Degree of Hearing Loss

- Determined on basis of the pure tone average (PTA) at 500, 1000, and 2000 Hz

Audiogram Legend for a Left Ear

- AC Unmasked
- BC Unmasked
- AC Masked
- BC Masked

Figure 16. Types of hearing loss and associated audiograms of a left ear

**PURE TONE PATTERNS**

1. **Conductive Hearing Loss** (Figure 16B and 16C)
   - BC in normal range
   - AC outside of normal range
   - Gap between AC and BC thresholds >10 dB (an air-bone gap)

2. **Sensorineural Hearing Loss** (Figure 16D and 16E)
   - Both air and bone conduction thresholds below normal
   - Gap between AC and BC <10 dB (no air-bone gap)

3. **Mixed Hearing Loss**
   - Both air and bone conduction thresholds below normal
   - Gap between AC and BC thresholds >10 dB (an air-bone gap)
Speech Audiometry

Speech Reception Threshold
- lowest hearing level at which patient is able to repeat 50% of two syllable words which have equal emphasis on each syllable (spondee words)
- SRT and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB; if not, suspect a retrocochlear lesion or functional hearing loss
- used to assess the reliability of the pure tone audiometry

Speech Discrimination Test
- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at 40 dB above the patient’s SRT, therefore degree of hearing loss is taken into account
- patients with normal hearing or conductive hearing loss score >90%
- score depends on extent of SNHL
- rollover effect: a decrease in discrimination as sound intensity increases; typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears as asymmetry may indicate a retrocochlear lesion
- used as best predictor of hearing aid response: a poor discrimination score indicates significant neural degeneration and hearing aids may not be the best option for the patient

Impedance Audiometry

Tympanogram
- the Eustachian tube equalizes the pressure between the external and middle ear
- tympanograms graph the compliance of the middle ear system against a pressure gradient ranging from to –400 to +200 mmH2O
- tympanogram peak occurs at the point of maximum compliance: where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range: –100 to +50 mmH2O

Figure 17. Tympanograms

Static Compliance
- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0.3-1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of >2 cc in children and 2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

Acoustic Stapedial Reflexes
- stapedius muscle contracts in response to loud sound
- acoustic reflex threshold = 70-100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
- stimulating either ear causes bilateral and symmetrical reflexes
- for reflex to be present, CN VII must be intact and no conductive hearing loss in monitored ear
- if reflex is absent without conductive or severe sensorineural loss, suspect CN VII lesion
- acoustic reflex decay test = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
- normally, little reflex decay occurs at 500 and 1000 Hz
- with cochlear hearing loss, acoustic reflex thresholds are 25-60 dB
- with retrocochlear hearing loss (acoustic neuroma), absent acoustic reflexes or marked reflex decay (>50%) within 5 s
Auditory Brainstem Response

- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (see Order of Neural Pathway sidebar on OT9); this test can be used to determine the site of lesion
- delay in brainstem response suggests cochlear or retrocochlear abnormalities
- does not require volition or co-operation of patient (therefore of value in children and in malingers)

Otoacoustic Emissions

- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- often used in newborn screening
- can be used to uncover normal hearing in malingering patients
- absence of emissions can be due to hearing loss or fluid in the middle ear

Aural Rehabilitation

- dependent on degree of hearing loss, communicative requirements, motivation, expectations, and physical and mental abilities
- negative prognostic factors
  - poor speech discrimination
  - narrow dynamic range (recruitment)
  - unrealistic expectations
- types of hearing aids
  - BTE: behind-the-ear (with occlusive mold or open fit which allows natural sound to pass – for milder hearing losses)
  - ITE: in-the-ear, placed in concha
  - ITC: in-the-canal, placed entirely in ear canal
  - CIC: contained-in-canal, placed deeply in ear canal
  - bone conduction – bone-anchored hearing aid (BAHA): attached to the skull
  - contralateral routing of signals (CROS)
- assistive listening devices
  - direct/indirect audio output
  - infrared, FM radio, or induction loop systems
  - telephone, television, or alerting devices
- cochlear implants
  - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
  - for profound bilateral sensorineural hearing loss not rehabilitated with conventional hearing aids
  - established indication: post-lingually deafened adults, pre- and post-lingually deaf children

Vertigo

Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
  - vertigo is produced by peripheral (inner ear) or central (brainstem-cerebellum) stimulation
  - it is important to distinguish vertigo from other disease entities that may present with similar complaints of “dizziness” (e.g. cardiovascular, psychiatric, neurological, aging)

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Peripheral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbalance</td>
<td>Moderate-severe</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Severe</td>
<td>Variable</td>
</tr>
<tr>
<td>Auditory Symptoms</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Neurologic Symptoms</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Compensation</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Unidirectional</td>
<td>Bidirectional</td>
</tr>
<tr>
<td></td>
<td>Horizontal or rotary</td>
<td>Horizontal or vertical</td>
</tr>
</tbody>
</table>
Table 6. Differential Diagnosis of Vertigo Based on History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
<th>Hearing Loss</th>
<th>Tinnitus</th>
<th>Aural Fullness</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Paroxysmal Positional Vertigo (BPPV)</td>
<td>Seconds</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Menière’s Disease</td>
<td>Minutes to hours</td>
<td>Uni/bilateral, fluctuating</td>
<td>Precedes attack</td>
<td>Pressure/warmth</td>
<td></td>
</tr>
<tr>
<td>Vestibular Neuronitis</td>
<td>Hours to days</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Recent AOM</td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>Days</td>
<td>Unilateral</td>
<td>Whistling</td>
<td>–</td>
<td>Ataxia CN VII palsy</td>
</tr>
<tr>
<td>Acoustic Neuroma</td>
<td>Chronic</td>
<td>Progressive</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Differential Diagnosis of Vertigo Based on Time Course

<table>
<thead>
<tr>
<th>Time Course</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent, lasting</td>
<td>BPPV</td>
</tr>
<tr>
<td>Single episode, lasting minutes to hours</td>
<td>Migraine, transient ischemia of the labyrinth or brainstem</td>
</tr>
<tr>
<td>Recurrent to hours</td>
<td>Menière’s</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Vestibular neuritis, MS, Brainstem/cerebellum infarct</td>
</tr>
</tbody>
</table>

Benign Paroxysmal Positional Vertigo

Definition
- acute attacks of transient rotatory vertigo lasting seconds to minutes initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)
- most common form of positional vertigo (50% of patients with peripheral vestibular dysfunction)

Etiology
- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
  - can affect each of the 3 semicircular canals, posterior canal is affected in >90% of cases
  - causes: head injury, viral infection (URTI), degenerative disease, idiopathic
  - results in slightly different signals being received by the brain from the two balance organs resulting in sensation of movement

Diagnosis
- history (time course, provoking factors, associative symptoms)
- positive Dix-Hallpike maneuver (sensitivity 82%, specificity 71%)

Dix-Hallpike Positional Testing (see website for video and illustrations)
- the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45° and neck extended 20° holding the position for 20 s
- onset of vertigo and rotary nystagmus indicate a positive test for the dependent side
- other diagnostic testing is not indicated in posterior canal BPPV

Treatment
- reassure patient that process resolves spontaneously
- particle repositioning maneuvers
  - Epley maneuver (performed by MD)
  - Brandt-Daroff exercises (performed by patient)
- surgery for refractory cases
- anti-emetics for nausea/vomiting
- drugs to suppress the vestibular system delay eventual recovery and are therefore not used

Menière’s Disease (Endolymphatic Hydrops)

Definition
- episodic attacks of tinnitus, hearing loss, aural fullness, and vertigo lasting minutes to hours

Proposed Etiology
- inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth

Diagnostic Criteria for Menière’s Disease (must have all three)
- Two spontaneous episodes of rotational vertigo ≥20 min
- Audiometric confirmation of SNHL (often low frequency)
- Tinnitus and/or aural fullness
Epidemiology
- peak incidence 40-60 yr
- bilateral in 35% of cases

Clinical Features
- episodic vertigo, fluctuating low frequency SNHL, tinnitus, and aural fullness
- ± drop attacks (Tumarkin crisis), ± N/V
- vertigo disappears with time (min to h), but hearing loss remains
- early in the disease: fluctuating SNHL
- later stages: persistent tinnitus and progressive hearing loss
- attacks come in clusters and can be debilitating to the patient
- triggers: high salt intake, caffeine, stress, nicotine, and alcohol

Treatment
- acute management may consist of bed rest, antiemetics, antivertiginous drugs, and low molecular weight dextrans (not commonly used)
- long-term management may include:
  - medical
    - low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
    - antivertiginous drugs prophylactically to decrease intensity of attacks
    - local application of gentamicin to destroy vestibular end-organ, results in complete SNHL
  - surgical
    - selective vestibular neurectomy or transtympanic labyrinthectomy
    - vestibular implants have recently been introduced, experimentally
- must monitor opposite ear as bilaterality occurs in 35% of cases

Vestibular Neuronitis

Definition
- acute onset of disabling vertigo often accompanied by nausea, vomiting, and imbalance without hearing loss that resolves over days leaving a residual imbalance that lasts days to weeks

Etiology
- thought to be due to a viral (e.g. measles, mumps, herpes zoster) or post viral inflammatory condition
- ~30% of cases have associated URTI symptoms
- other: microvascular events, diabetes, autoimmune process
- considered to be the vestibular equivalent of Bell's palsy, sudden hearing loss, and acute vocal cord palsy

Clinical Features
- acute phase
  - severe vertigo with nausea, vomiting, and imbalance lasting 1-5 d
  - irritative nystagmus (fast phase towards the offending ear)
  - patient tends to veer towards affected side
- convalescent phase
  - imbalance and motion sickness lasting days to weeks
  - spontaneous nystagmus away from affected side
  - gradual vestibular adaptation requires weeks to months
- incomplete recovery likely with the following risk factors: elderly, visual impairment, poor ambulation
- repeated attacks can occur

Treatment
- acute phase
  - bed rest, vestibular sedatives dimenhydrinate, diazepam
- convalescent phase
  - progressive ambulation especially in the elderly
  - vestibular exercises: involve eye and head movements, sitting, standing, and walking

Labyrinthitis

Definition
- acute infection of the inner ear resulting in vertigo and hearing loss

Etiology
- may be serous (viral) or purulent (bacterial)
- occurs as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures
- bacterial: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *P. aeruginosa*, *P. mirabilis*
- viral: rubella, CMV, measles, mumps, varicella zoster

Drop Attacks (Tumarkin’s Otolithic Crisis) are sudden falls occurring without warning and without LOC

Before proceeding with gentamicin treatment, perform a gadolinium enhanced MRI to rule out CPA tumor as the cause of symptoms
Clinical Features
• sudden onset of vertigo, N/V, tinnitus, and unilateral hearing loss with no associated fever or pain
• meningitis is a serious complication

Investigations
• CT head
• if meningitis is suspected: lumbar puncture, blood cultures

Treatment
• treat with IV antibiotics, drainage of middle ear ± mastoidectomy

**Acoustic Neuroma (Vestibular Schwannoma)**

Definition
• schwannoma of the vestibular portion of CN VIII

Pathogenesis
• starts in the internal auditory canal and expands into cerebellopontine angle (CPA), compressing cerebellum and brainstem
• when associated with type 2 neurofibromatosis (NF2): bilateral acoustic neuromas, café-au-lait skin lesions, and multiple intracranial lesions

Clinical Features
• usually presents with unilateral SNHL (chronic) or tinnitus
• dizziness and unsteadiness may be present, but true vertigo is rare as tumor growth occurs slowly and thus compensation occurs
• facial nerve palsy and trigeminal (V1) sensory deficit (corneal reflex) are late complications
• risk factors: exposure to loud noise, childhood exposure to low-dose radiation, history of parathyroid adenoma

Diagnosis
• MRI with gadolinium contrast (gold standard)
• audiogram (to assess SNHL)
• poor speech discrimination relative to the hearing loss
• stapedial reflex absent or significant reflex decay
• ABR: increase in latency of the 5th wave
• vestibular tests: normal or asymmetric caloric weakness (an early sign)

Treatment
• expectant management if tumor is very small, or in elderly
• definitive management is surgical excision
• other options: gamma knife, radiation

**Tinnitus**

Definition
• an auditory perception in the absence of an acoustic stimuli, likely related to loss of input to neurons in central auditory pathways and resulting in abnormal firing

History
• subjective vs. objective (Figure 14, OT7)
• continuous vs. pulsatile (vascular in origin)
• unilateral vs. bilateral
• associated symptoms: hearing loss, vertigo, aural fullness, otalgia, otorrhea

Investigations
• audiology
• if unilateral
  • ABR, gadolinium enhanced MRI to exclude a retrocochlear lesion
  • CT to diagnose glomus tympanicum (rare)
  • MRI or angiogram to diagnose AVM
• if suspect metabolic abnormality: lipid profile, TSH

Treatment
• if a cause is found, treat the cause (e.g. drainage of middle ear effusion, embolization or excision of AVM)
• with no treatable cause: 50% will improve, 25% worsen, 25% remain the same
• avoid loud noise, ototoxic meds, caffeine, smoking
• tinnitus clinics
• identify situations where tinnitus is most bothersome (e.g. quiet times), mask tinnitus with soft music or “white noise”
• hearing aid if coexistent hearing loss
• tinnitus instrument: combines hearing aid with white noise masker
• trial of tocainamide

**Diseases of the External Ear**

### Cerumen Impaction

**Etiology**
- ear wax: a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

**Risk Factors**
- hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

**Clinical Features**
- hearing loss (conductive)
- ± tinnitus, vertigo, otalgia, aural fullness

**Treatment**
- ceruminolytic drops (bicarbonate solution, olive oil, glycerine, Cerumenex®)
- syringing
- manual débridement (by MD)

### Exostoses

**Definition**
- bony protuberances in the external auditory canal composed of lamellar bone

**Etiology**
- possible association with swimming in cold water

**Clinical Features**
- usually an incidental finding
- if large, they can cause cerumen impaction or otitis externa

**Treatment**
- no treatment required unless symptomatic

### Otitis Externa

**Etiology**
- bacteria (~90% of OE): *Pseudomonas aeruginosa*, *Pseudomonas vulgaris*, *E. coli*, *S. aureus*
- fungus: *Candida albicans*, *Aspergillus niger*

**Risk Factors**
- associated with swimming (“swimmer’s ear”)
- mechanical cleaning (Q-tips®), skin dermatitis, aggressive scratching
- devices that occlude the ear canal: hearing aids, headphones, etc.
- allergic contact dermatitis, dermatologic conditions (psoriasis, atopic dermatitis)

**Clinical Features**
- acute
  - pain aggravated by movement of auricle (traction of pinna or pressure over tragus)
  - otorrhea (sticky yellow purulent discharge)
  - conductive hearing loss ± aural fullness 2nd to obstruction of external canal by swelling and purulent debris
  - posterior auricular lymphadenopathy
  - complicated OE exists if the pinna and/or the periauricular soft tissues are erythematous and swollen
- chronic
  - pruritus of external ear ± excoriation of ear canal
  - atrophic and scaly epidermal lining, ± otorrhea, ± hearing loss
  - wide meatus but no pain with movement of auricle
  - tympanic membrane appears normal

---

Cerumen impaction is the most common cause of conductive hearing loss for those aged 15-50 yr

Syringing

**Indications**
- Totally occlusive cerumen with pain, decreased hearing, or tinnitus

**Contraindications**
- Active infection
- Previous ear surgery
- Only hearing ear
- TM perforation

**Complications**
- Otitis externa
- TM perforation
- Trauma
- Pain
- Vertigo
- Tinnitus
- Otitis media

**Method**
- Establish that TM is intact
- Gently pull the pinna superiorly and posteriorly
- Using warm water, aim the syringe nozzle upwards and posteriorly to irrigate the ear canal

Pulling on the pinna is extremely painful in otitis externa, but is usually well tolerated in otitis media
Treatment
- clean ear under magnification with irrigation, suction, dry swabbing, and C&S
- bacterial etiology
  - antipseudomonal otic drops (e.g. ciprofloxacin) or a combination of antibiotic and steroid (e.g. Cipro HC®)
  - do not use aminoglycoside if the tympanic membrane (TM) is perforated because of the risk of ototoxicity
  - introduction of fine gauze wick (pope wick) if external canal edematous
  - ± 3% acetic acid solution to acidify ear canal (low pH is bacteriostatic)
  - systemic antibiotics if either cervical lymphadenopathy or cellulitis is present
- fungal etiology
  - repeated debridement and topical antifungals (gentian violet, Mycostatin® powder, boric acid, clioquinol-flumetasone drops)
  - ± analgesics
- chronic otitis externa (pruritus without obvious infection) → corticosteroid alone (e.g. diprosalic acid)

Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

Definition
- osteomyelitis of the temporal bone

Epidemiology
- occurs in elderly diabetics and immunocompromised patients

Etiology
- rare complication of otitis externa
- *Pseudomonas* infection in 99% of cases

Clinical Features
- otalgia and purulent otorrhea that is refractory to medical therapy
- granulation tissue on the floor of the auditory canal

Complications
- cranial nerve palsy (most commonly VII>X>XI)
- systemic infection, death

Management
- imaging: high resolution temporal bone CT scan, gadolinium enhanced MRI, technetium scan
- requires hospital admission, debridement, IV antibiotics, hyperbaric O₂
- may require OR for debridement of necrotic tissue/bone

Diseases of the Middle Ear

Acute Otitis Media and Otitis Media with Effusion
- see *Pediatric Otolaryngology*, OT39

Chronic Otitis Media

Definition
- an ear with TM perforation in the setting of recurrent or chronic ear infections

Benign
- dry TM perforation without active infection

Chronic Serous Otitis Media
- continuous serous drainage (straw-colored)

Chronic Suppurative Otitis Media
- persistent purulent drainage through a perforated TM
**Cholesteatoma**

**Definition**
- a cyst composed of keratinized desquamated epithelial cells occurring in the middle ear, mastoid, and temporal bone
- two types: congenital and acquired

**Congenital**
- presents as a “small white pearl” behind an intact tympanic membrane (anterior and medial to the malleus) or as a conductive hearing loss
- believed to be due to aberrant migration of external canal ectoderm during development
- not associated with otitis media/Eustachian tube dysfunction

**Acquired (more common)**
- generally occurs as a consequence of otitis media and chronic Eustachian tube dysfunction
- primary cholesteatoma
  - frequently associated with retraction pockets in the pars flacida (may lead to attic cholesteatomas which are difficult to visualize)
  - often has crusting or desquamated debris on lateral surface
- secondary cholesteatoma
  - pearly mass evident behind TM, frequently associated with marginal perforation
  - may appear as skin that have replaced the mucosa of the middle ear
- the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

**Clinical Features**
- history of otitis media (especially if unilateral), ventilation tubes, ear surgery
- symptoms
  - progressive hearing loss (predominantly conductive although may get sensorineural hearing loss in late stage)
  - otalgia, aural fullness, fever
- signs
  - retraction pocket in TM, may contain keratin debris
  - TM perforation
  - granulation tissue, polyp visible on otoscopy
  - malodorous, unilateral otorrhoea

**Complications**

<table>
<thead>
<tr>
<th>Local Complication</th>
<th>Intracranial Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ossicular erosion: conductive hearing loss</td>
<td>Meningitis</td>
</tr>
<tr>
<td>Inner ear erosion: SNHL, dizziness, and/or labyrinthitis</td>
<td>Sigmoid sinus thrombosis</td>
</tr>
<tr>
<td>Temporal bone infection: mastoiditis, petrositis</td>
<td>Intracranial abscess (subdural, epidural, cerebellar)</td>
</tr>
</tbody>
</table>

**Investigations**
- audiogram and CT scan

**Treatment**
- there is no conservative therapy for cholesteatoma
- surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction

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**Mastoiditis**

**Definition**
- infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two weeks after onset of untreated or inadequately treated acute suppurative otitis media
- more common in children than adults

**Etiology**
- acute mastoiditis caused by the same organisms as AOM: **S. pneumoniae, H. influenzae, M. catarrhalis, S. pyogenes, S. aureus, P. aeruginosa**

**Clinical Features**
- otorrhea
- tenderness to pressure over the mastoid
- retroauricular swelling with protruding ear
- fever, hearing loss, ± TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)
Treatment
- IV antibiotics with myringotomy and ventilation tubes – usually all that is required acutely
- cortical mastoidectomy
  - debridement of infected tissue allowing aeration and drainage
- indications for surgery
  - failure of medical treatment after 48 h
  - symptoms of intracranial complications
  - aural discharge persisting for 4 wk and resistant to antibiotics

**Otosclerosis**

**Definition**
- fusion of stapes footplate to oval window so that it cannot vibrate

**Etiology**
- autosomal dominant, variable penetrance approximately 40%
- F>M, progresses during pregnancy (hormone responsive)

**Clinical Features**
- progressive conductive hearing loss first noticed in teens and 20s (may progress to sensorineural hearing loss if cochlea involved)
- ± pulsatile tinnitus
- tympanic membrane normal ± pink blush (Schwartz’s sign) associated with the neovascularization of otosclerotic bone
- characteristic dip at 2000 Hz (Carhart's notch) on audiogram (Figure 16C, OT110)

**Treatment**
- monitor with serial audiograms if coping with loss
- hearing aid (air conduction, bone conduction, BAHA)
- stapedectomy or stapedotomy (with laser or drill) with prosthesis is definitive treatment

**Diseases of the Inner Ear**

**Congenital Sensorineural Hearing Loss**

**Hereditary Defects**
- non-syndrome associated (70%)
  - often idiopathic, autosomal recessive
  - connexin 26 (GJB2) most common
- syndrome associated (30%)
  - Waardenburg: white forelock, heterochromia iridis (each eye different color), wide nasal bridge and increased distance between medial canthi
  - Pendred: deafness associated with thyroid gland disorders, SLC26A4 gene, enlarged vestibular aqueducts
  - Treacher-Collins: first and second branchial cleft anomalies
  - Alport: hereditary nephritis

**Prenatal TORCH Infections**
- toxoplasmosis, others (e.g. HIV, syphilis), rubella, CMV, HSV

**Perinatal**
- Rh incompatibility
- anoxia
- hyperbilirubinemia
- birth trauma (hemorrhage into inner ear)

**Postnatal**
- meningitis, mumps, measles

**High Risk Factors (for hearing loss in newborns)**
- low birth weight/prematurity
- perinatal anoxia (low APGARs)
- kernicterus: bilirubin >25 mg/dL
- craniofacial abnormality
- family history of deafness in childhood
- 1st trimester illness: TORCH infections
- neonatal sepsis
- ototoxic drugs
perinatal infection, including post-natal meningitis
- consanguinity
- 50-75% of newborns with SNHL have at least one of the above risk factors and 90% of these have spent time in the NICU
- presence of any risk factor: ABR study performed before leaving NICU and at 3 mo adjusted age
- early rehabilitation improves speech and school performance

### Presbycusis

**Definition**
- SNHL associated with aging (starting in 5th and 6th decades)

**Etiology**
- hair cell degeneration
- age related degeneration of basilar membrane, possibly genetic etiology
- cochlear neuron damage
- ischemia of inner ear

**Clinical Features**
- progressive, bilateral hearing loss initially at high frequencies, then middle frequencies
- loss of discrimination of speech especially with background noise present – patients describe people as mumbling
- recruitment phenomenon: inability to tolerate loud sounds
- tinnitus

**Treatment**
- hearing aid if patient has difficulty functioning, hearing loss >30-35 dB, and good speech discrimination
- ± lip reading, auditory training, auditory aids (doorbell and phone lights)

### Sudden Sensorineural Hearing Loss

**Clinical Features**
- presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, aural fullness
- usually idiopathic, rule out other causes
  - autoimmune causes (e.g. ESR, rheumatoid factor, ANA)
  - MRI to rule out tumor and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)

**Treatment**
- oral corticosteroids within 3 d of onset: prednisone 1 mg/kg/d for 10-14 d

**Prognosis**
- depends on degree of hearing loss
- 70% resolve within 10-14 d
- 20% experience partial resolution
- 10% experience permanent hearing loss

### Autoimmune Inner Ear Disease

**Etiology**
- idiopathic
- may be associated with systemic autoimmune diseases (e.g. rheumatoid arthritis, SLE), vasculitides (e.g. GPA, polyarteritis nodosa), and allergies

**Epidemiology**
- most common between ages 20-50

**Clinical Features**
- rapidly progressive or fluctuating bilateral SNHL
- ± tinnitus, aural fullness, vestibular symptoms (i.e. ataxia, disequilibrium, vertigo)

**Investigations**
- autoimmune workup: CBC, ESR, ANA, rheumatoid factor
**Treatment**
- high-dose corticosteroids: treat early for at least 30 d
- consider cytotoxic medication for steroid non-responders

**Drug Ototoxicity**

**Aminoglycosides**
- streptomycin and gentamicin (vestibulotoxic), kanamycin, and tobramycin (cochleotoxic)
- toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
- destroys sensory hair cells: outer first, inner second (therefore otoacoustic emissions are lost first)
- high frequency hearing loss develops earliest
- ototoxicity occurs days to weeks post-treatment
- must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
- q24h dosing recommended (with amount determined by creatinine clearance)
- aminoglycoside toxicity displays saturable kinetics, therefore, once daily dosing presents less risk than divided daily doses
- duration of treatment is the most important predictor of ototoxicity
- treatment: immediately stop aminoglycosides

**Salicylates**
- hearing loss with tinnitus, reversible if discontinued

**Antimalarials (Quinines)**
- hearing loss with tinnitus
- reversible if discontinued but can lead to permanent loss

**Others**
- many antineoplastic agents are ototoxic (weigh risks vs. benefits)
- loop diuretics

**Noise-Induced Sensorineural Hearing Loss**

**Pathogenesis**
- 85-90 dB over months or years or single sound impulses >135 dB can cause cochlear damage
- bilateral SNHL initially and most prominently at 4000 Hz (resonant frequency of the temporal bone), known as "boilermaker's notch" on audiogram, extends to higher and lower frequencies with time (see Figure 16D, OT10)
- speech reception not altered until hearing loss >30 dB at speech frequency, therefore considerable damage may occur before patient complains of hearing loss
- difficulty with speech discrimination, especially in situations with competing noise

**Phases of Hearing Loss**
- dependent on: intensity of sound and duration of exposure
  - temporary threshold shift
    - when exposed to loud sound, decreased sensitivity or increased threshold for sound
    - may have associated aural fullness and tinnitus
    - with removal of noise, hearing returns to normal
  - permanent threshold shift
    - hearing does not return to previous state

**Treatment**
- hearing aid
- prevention
  - ear protectors: muffs, plugs
  - limit exposure to noise with frequent rest periods
  - regular audiologic follow-up
**Temporal Bone Fractures**

### Table 9. Features of Temporal Bone Fractures

<table>
<thead>
<tr>
<th></th>
<th>Transverse (1)</th>
<th>Longitudinal (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extension</strong></td>
<td>Into bony labyrinth and internal auditory meatus</td>
<td>Into middle ear</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>10-20%</td>
<td>70-90%</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Frontal/occipital trauma</td>
<td>Lateral skull trauma</td>
</tr>
<tr>
<td><strong>CN Pathology</strong></td>
<td>CN VII palsy (50%)</td>
<td>CN VII palsy (10-20%)</td>
</tr>
<tr>
<td><strong>Hearing Loss</strong></td>
<td>SNHL due to direct cochlear injury</td>
<td>CHL secondary to ossicular injury</td>
</tr>
<tr>
<td><strong>Vestibular Symptoms</strong></td>
<td>Sudden onset vestibular symptoms due to direct</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>semicircular canal injury (vertigo, spontaneous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nystagmus)</td>
<td></td>
</tr>
<tr>
<td><strong>Other Features</strong></td>
<td>Intact external auditory meatus, TM ± hemotympanum</td>
<td>Tom TM or hemotympanum</td>
</tr>
<tr>
<td></td>
<td>Spontaneous nystagmus</td>
<td>Bleeding from external auditory canal</td>
</tr>
<tr>
<td></td>
<td>CSF leak in Eustachian tube to nasopharynx ±</td>
<td>Step formation in external auditory canal</td>
</tr>
<tr>
<td></td>
<td>rhinorrhea (risk of meningitis)</td>
<td>CSF otorrhoe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Battle’s sign = mastoid ecchymoses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raccoon eyes = periorbital ecchymoses</td>
</tr>
</tbody>
</table>

- characterized as longitudinal or transverse relative to the long axis of the petrous temporal bone
- temporal bone fractures are rarely purely transverse or longitudinal (often a mixed picture)

**Diagnosis**
- otoscopy
- do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
- CT head
- audiology, facial nerve tests (for transverse fractures), Schirmer’s test (of lacrimation), stapedial reflexes if CN VII palsy
- if suspecting CSF leak: look for halo sign, send fluid for β-2 transferrin

**Treatment**
- ABCs
- medical: expectant, prevent otogenic meningitis
- surgical: explore temporal bone, indications:
  - CN VII palsy (immediate and complete)
  - gunshot wound
  - depressed fracture of external auditory meatus
  - early meningitis (mastoidectomy)
  - bleeding intracranially from sinus
  - CSF otorrhoea (may resolve spontaneously)

**Complications**
- AOM ± labyrinthitis ± mastoiditis
- meningitis/epidural abscess/brain abscess
- post-traumatic cholesteatoma

---

**Facial Nerve (CN VII) Paralysis**

**Etiology**
- supranuclear and nuclear (MS, poliomyelitis, cerebral tumors)
- infranuclear

**Treatment**
- treat according to etiology plus provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, gold weighting of upper lid
- facial paralysis that does not resolve with time or with medical treatment will often be referred for possible reanimation techniques to restore function
  - common reanimation techniques include
    - direct facial nerve anastomosis
    - interpositional grafts
    - anastomosis to other motor nerves
    - muscle transpositions

---

**Figure 18. Types of temporal bone fractures**

- Signs of Basilar Skull Fracture
  - Battle’s Sign: ecchymosis of the mastoid process of the temporal bone
  - Raccoon Eyes
  - CSF Rhinorrhea/Otorrhea
  - Cranial Nerve Involvement: facial palsy → CN VII, nystagmus → CN VI, facial numbness → CN V

- The halo sign: the double ringed appearance of CSF fluid on white filter paper as it separates out from blood

- Hemotympanum can be indicative of temporal bone trauma

- House-Brackmann Facial Nerve Grading System
  - Grade I: Normal facial motor function
    - Slight weakness
    - Normal symmetry and tone at rest
    - Complete eye closure
  - Grade II: Mild dysfunction
    - Obvious weakness
    - Disfiguring asymmetry
    - Incomplete eye closure
    - No forehead motion
    - Mouth asymmetric motion
  - Grade III: Moderate dysfunction
    - Obvious weakness
    - Severe dysfunction
    - Barely perceptible motion of mouth
    - Asymmetric at rest
  - Grade IV: Total paralysis
    - No movement
Table 10. Differential Diagnosis of Peripheral Facial Paralysis (PFP)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incidence</th>
<th>Findings</th>
<th>Investigations</th>
<th>Treatment, Follow-up, and Prognosis (Px)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell’s Palsy</td>
<td>80-90% of PFP</td>
<td>Hx: Acute onset; numbness of ear; Schirmer’s test</td>
<td>Stapedial reflex absent; audiometry normal (or baseline); EMG – best measure for prognosis; topographic testing; MRI with gadolinium enhancement of CN VII and VIII; high resolution CT</td>
<td>Rx: Protect the eye to prevent exposure keratitis with patching or tarsorraphy; systemic steroids may lessen degeneration and hasten recovery; consider antiviral (acyclovir) F/U: Spontaneous remission should begin within 3 wk of onset; delayed (3-6 mo) recovery portends at least some functional loss Px: &gt;90% recover spontaneously and completely overall; &gt;90% recovery if paralysis was incomplete Poorer if hyperacusis, &gt;60 yr, DM, HTN, severe pain</td>
</tr>
<tr>
<td>Ramsay Hunt Syndrome (Herpes Zoster Oticus)</td>
<td>4.5-9% of PFP</td>
<td>Hx: Hyperacusis; SNHL; severe pain of pinna, mouth, or face; vesicles on pinna, external canal (rupture 3-7 d after onset of pain); associated herpes zoster ophthalmicus (uveitis, keratoconjunctivitis, optic neuritis, or glaucoma)</td>
<td>Stapedial reflex absent; audiometry – SNHL; viral ELISA studies to confirm MRI with gadolinium (86% of facial nerves enhance)</td>
<td>Rx: Avoid touching lesions to prevent spread of infection; systemic steroids can relieve pain, vertigo, avoid postherpetic neuralgia; Acyclovir may lessen pain, aid healing of vesicles; F/U: 2-4 wk Px: Poorer prognosis than Bell’s palsy; 22% recover completely, 66% incomplete paralysis</td>
</tr>
<tr>
<td>Temporal Bone Fracture</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal (90%)</td>
<td>20% have PFP</td>
<td>Hx: Blow to side of head; trauma to side of head; neuro findings consistent with epidural/subdural bleed</td>
<td>Skull x-rays CT head</td>
<td>Px: Injury usually due to stretch or impingement; may recover with time</td>
</tr>
<tr>
<td>Transverse (10%)</td>
<td>40% have PFP</td>
<td>Hx: Blow to frontal or occipital area; trauma to front or back of head</td>
<td>Skull x-rays CT head</td>
<td>Px: Nerve transection more likely</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Variable depending on level of injury</td>
<td></td>
<td>Wait for lidocaine to wear off EMG</td>
<td>Rx: Exploration if complete nerve paralysis; no exploration if any movement present</td>
</tr>
</tbody>
</table>

Source: Paul Warrick, MD

Rhinitis

Definition
- inflammation of the lining (mucosa) of the nasal cavity

Table 11. Classification of Rhinitis

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Perennial non-allergic</td>
<td>• Rhinitis medicamentosa</td>
</tr>
<tr>
<td>• Asthma, ASA sensitivity</td>
<td>• Topical decongestants</td>
</tr>
<tr>
<td>• Allergic</td>
<td>• Hormonal</td>
</tr>
<tr>
<td>• Seasonal</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td>• Perennial</td>
<td>• Estrogens</td>
</tr>
<tr>
<td>• Atrophic</td>
<td>• Thyroid</td>
</tr>
<tr>
<td>• Primary: Klebsiella ozena (especially in elderly)</td>
<td>• Idiopathic vasomotor</td>
</tr>
<tr>
<td>• Acquired: post-surgery if too much mucosa or turbinate has been resected</td>
<td></td>
</tr>
<tr>
<td>• Infectious</td>
<td></td>
</tr>
<tr>
<td>• Viral: e.g. rhinovirus, influenza, parainfluenza, etc.</td>
<td></td>
</tr>
<tr>
<td>• Bacterial: e.g. S. aureus</td>
<td></td>
</tr>
<tr>
<td>• Fungal</td>
<td></td>
</tr>
<tr>
<td>• Granulomatous: TB, syphilis, leprosy</td>
<td></td>
</tr>
<tr>
<td>• Non-infectious</td>
<td></td>
</tr>
<tr>
<td>• Sarcoedosis</td>
<td></td>
</tr>
<tr>
<td>• GPA</td>
<td></td>
</tr>
<tr>
<td>• Irritant</td>
<td></td>
</tr>
<tr>
<td>• Dust</td>
<td></td>
</tr>
<tr>
<td>• Chemicals</td>
<td></td>
</tr>
<tr>
<td>• Pollution</td>
<td></td>
</tr>
</tbody>
</table>

Rhinitis medicamentosa: rebound congestion due to the overuse of intranasal vasoconstrictors; for prevention, use of these medications for only 5-7 d is recommended
### Table 12. Nasal Discharge: Character and Associated Conditions

<table>
<thead>
<tr>
<th>Character</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery/mucoid</td>
<td>Allergic, viral, vasomotor, CSF leak (halo sign)</td>
</tr>
<tr>
<td>Mucopurulent</td>
<td>Bacterial, foreign body</td>
</tr>
<tr>
<td>Serosanguinous</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Bloody</td>
<td>Trauma, neoplasia, bleeding disorder, HTN/vascular disease</td>
</tr>
</tbody>
</table>

### Allergic Rhinitis (Hay Fever)

**Definition**
- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds

**Etiology**
- when allergens contact the respiratory mucosa, specific IgE antibody is produced in susceptible hosts
- concentration of allergen in the ambient air correlates directly with the rhinitis symptoms

**Epidemiology**
- age at onset usually <20 yr
- more common in those with a personal or family history of allergies/atopy

**Clinical Features**
- nasal: obstruction with pruritus, sneezing
- clear rhinorrhea (containing increased eosinophils)
- itching of eyes with tearing
- frontal headache and pressure
- mucosa: swollen, pale, “boggy”
- seasonal (summer, spring, early autumn)
  - pollens from trees
  - lasts several weeks, disappears, and recurs following year at same time
- perennial
  - inhaled: house dust, wool, feathers, foods, tobacco, hair, mold
  - ingested: wheat, eggs, milk, nuts
  - occurs intermittently for years with no pattern or may be constantly present

**Complications**
- chronic sinusitis/polyps
- serous otitis media

**Diagnosis**
- history
- direct exam
- allergy testing

**Treatment**
- education: identification and avoidance of allergen
- nasal irrigation with saline
- antihistamines (e.g. diphenhydramine, fexofenadine)
- oral decongestants (e.g. pseudoephedrine, phenylpropanolamine)
- topical decongestant (may lead to rhinitis medicamentosa)
- other topicalics: steroids (fluticasone), disodium cromoglycate, antihistamines, ipratropium bromide
- oral steroids if severe
- desensitization by allergen immunotherapy

Congestion reduces nasal airflow and allows the nose to repair itself (i.e. washes away the irritants) Treatment should focus on the initial insult rather than target this defense mechanism.
Vasomotor Rhinitis

- neurovascular disorder of nasal parasympathetic system (vidian nerve) affecting mucosal blood vessels
- nonspecific reflex hypersensitivity of nasal mucosa
- caused by:
  - temperature change
  - alcohol, dust, smoke
  - stress, anxiety, neurosis
  - endocrine: hypothyroidism, pregnancy, menopause
  - parasympathomimetic drugs
  - beware of rhinitis medicamentosa: reactive vasodilation due to prolonged use (>5 d) of nasal drops and sprays

Clinical Features

- chronic intermittent nasal obstruction, varies from side to side
- rhinorrhea: thin, watery
- mucosa and turbinates: swollen
- nasal allergy must be ruled out

Treatment

- elimination of irritant factors
- parasympathetic blocker (Atrovent® nasal spray)
- steroids (e.g. beclomethasone, fluticasone)
- surgery (often of limited lasting benefit): electrocautery, cryosurgery, laser treatment, or removal of inferior or middle turbinates
- vidian neurectomy (rarely done)
- symptomatic relief with exercise (increased sympathetic tone)

Rhinosinusitis

Pathogenesis of Rhinosinusitis

- ostial obstruction or dysfunctional cilia permit stagnant mucous and, consequently, infection
- all sinuses drain to a common prechamber under the middle meatus called the osteomeatal complex

Definition

- inflammation of the mucosal lining of the sinuses and nasal passages

Classification

- acute: <4 wk
- subacute: 4-8 wk
- chronic: >8-12 wk

Table 13. Etiologies of Rhinosinusitis

<table>
<thead>
<tr>
<th>Ostial Obstruction</th>
<th>Inflammation</th>
<th>Allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>Septal deviation</td>
<td>Turbinate hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Polyps</td>
<td>Tumors</td>
</tr>
<tr>
<td></td>
<td>Adenoid hypertrophy</td>
<td>Foreign body</td>
</tr>
<tr>
<td></td>
<td>Congenital abnormalities (e.g. cleft palate)</td>
<td>GPA</td>
</tr>
<tr>
<td>Immune</td>
<td>Lymphoma, leukemia</td>
<td>Immunosuppressed patients (e.g. neutropenics, diabetics, HIV)</td>
</tr>
</tbody>
</table>

Systemic

- Cystic fibrosis
- Immotile cilia (e.g. Kartagener’s)

Direct Extension

- Dental: Infection
- Trauma: Facial fractures
### Acute Bacterial Rhinosinusitis

**Definition**
- bacterial infection of the paranasal sinuses and nasal passages lasting >7 d
- clinical diagnosis requiring ≥2 major symptoms, at least one of the symptoms is either nasal obstruction or purulent/discolored nasal discharge

**Major symptoms**
- facial pain/pain pressure/fullness
- nasal obstruction
- purulent/discolored nasal discharge
- hyposmia/anosmia

**Minor symptoms**
- headache
- halitosis
- fatigue
- dental pain
- cough
- ear pain/fullness

**Etiology**
- bacteria: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis, S. aureus*, anaerobes (dental)
- children are more prone to a bacterial etiology, but viral is still more common
- maxillary sinus most commonly affected
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless, black or pale mucosa on examination)

**Clinical Features**
- sudden onset of
  - nasal blockage/congestion and/or purulent nasal discharge/posterior nasal drip
  - ± facial pain or pressure, hyposmia, sore throat
- persistent/worsening symptoms >5-7 d or presence of purulence for 3-4 d with high fever
- speculum exam: erythematous mucosa, mucopurulent discharge, pus originating from the middle meatus
- predisposing factors: viral URTI, allergy, dental disease, anatomical defects
- differentiate from acute viral rhinosinusitis (course: <10 d, peaks by 3 d)

**Management**
- depends on symptom severity (i.e. intensity/duration of symptoms, impact on quality of life)
- mild-moderate: INCS
- if no response within 72 h, add antibiotics
- severe: INCS + antibiotics
- antibiotics
  - 1st line: amoxicillin x 10 d (TMP-SMX or macrolide if penicillin allergy)
  - if no response to 1st line antibiotics within 72 h, switch to 2nd line
- adjuvant therapy (saline irrigation, analgesics, oral/topical decongestant) may provide symptomatic relief
- CT indicated only if complications are suspected

### Chronic Rhinosinusitis

**Definition**
- inflammation of the mucosa of paranasal sinuses and nasal passages >8-12 wk
- diagnosis requiring ≥2 major symptoms for >8-12 wk and ≥1 objective finding of inflammation of the paranasal sinuses (CT/endoscopy)

**Etiology**
- unclear etiology but the following may contribute or predispose:
  - inadequate treatment of acute rhinosinusitis
  - bacterial colonization/biofilms
    - *S. aureus, enterobacteriaceae, Pseudomonas, S. pneumoniae, H. influenzae, β-hemolytic streptococci*
  - fungal infection (e.g. *Aspergillus, Zygomycetes, Candida*)
  - anatomic abnormality (e.g. lost ostia patency, deviated septum – predisposing factors)
  - allergy/allergic rhinitis
  - ciliary disorder (e.g. cystic fibrosis, Kartagener syndrome)
  - chronic inflammatory disorder (e.g. GPA)
  - untreated dental disease

---

**Acute Rhinosinusitis Complications**
Consider hospitalization if any of the following are suspected
- **Orbital (Chandler’s classification)**
  - Subperiosteal abscess
  - Orbital abscess
  - Cavernous sinus thrombosis
- **Intracranial**
  - Meningitis
  - Abscess
  - Bony
  - Subperiosteal frontal bone abscess (“Pott’s Puffy tumor”)
  - Osteomyelitis
- **Neurologic**
  - Superior orbital fissure syndrome (CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypesthesia)
  - Orbital apex syndrome (as above, plus neuritis, papilledema, decreased visual acuity)

**FESS = Functional Endoscopic Sinus Surgery**
Opening of the entire osteomeatal complex in order to facilitate drainage while sparing the sinus mucosa

**Allergic fungal rhinosinusitis is a chronic sinusitis affecting mostly young, immunocompetent, atopic individuals. Treatment options include FESS ± intranasal topical steroids, antifungals, and immunotherapy**
Clinical Features (similar to acute, but less severe)
- chronic nasal obstruction
- purulent anterior/posterior nasal discharge
- facial congestion/fullness
- facial pain/pressure
- hyposmia/anosmia
- halitosis
- chronic cough
- maxillary dental pain

Management
- identify and address contributing or predisposing factors
- obtain CT or perform endoscopy
- if polyps present: INCS, oral steroids ± antibiotics (if signs of infection), refer to otolaryngologist/H&N surgeon
- if polyps absent: INCS, antibiotics, saline irrigation, oral steroids (severe cases)
- antibiotics for 3-6 wk
  - amoxillin-clavulanic acid inhibitors, fluoroquinolone (moxifloxacin), macrolide (clarithromycin), clindamycin, Flagyl® (metronidazole)
- surgery if medical therapy fails or fungal sinusitis: FESS, balloon sinoplasty

Complications
- same as acute sinusitis, mucocele

Epistaxis

Blood Supply to the Nasal Septum (see Figure 4, OT3)
1. Superior posterior septum
   - internal carotid → ophthalmic → anterior/posterior ethmoidal
2. Posterior septum
   - external carotid → internal maxillary → sphenopalatine artery → nasopalatine
3. Lower anterior septum
   - external carotid → facial artery → superior labial artery → nasal branch
   - external carotid → internal maxillary → descending palatine → greater palatine
- these arteries all anastomose to form Kiesselbach’s plexus, located at Little’s area (anterior-inferior portion of the cartilaginous septum)
- bleeding from above middle turbinate is internal carotid, and from below is external carotid

Table 14. Etiology of Epistaxis

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Tumors</td>
</tr>
<tr>
<td></td>
<td>- Benign: polyps, inverting papilloma, angiofibroma</td>
</tr>
<tr>
<td></td>
<td>- Malignant: SCC, esthesioneuroblastoma (olfactory neuroblastoma)</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>- Rhinitis: allergic, non-allergic</td>
</tr>
<tr>
<td></td>
<td>- Infections: bacterial, viral, fungal</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Systemic</td>
<td>Coagulopathies</td>
</tr>
<tr>
<td></td>
<td>- Meds: anticoagulants, NSAIDs</td>
</tr>
<tr>
<td></td>
<td>- Hemophilia, von Willebrand’s</td>
</tr>
<tr>
<td></td>
<td>- Hematological malignancies</td>
</tr>
<tr>
<td></td>
<td>- Liver failure, uremia</td>
</tr>
<tr>
<td></td>
<td>Vascular: HTN, atherosclerosis, Osler-Weber-Weiss</td>
</tr>
<tr>
<td></td>
<td>(hereditary hemorrhagic telangiectasia)</td>
</tr>
<tr>
<td></td>
<td>Others: GPA, SLE</td>
</tr>
</tbody>
</table>

Investigations
- CBC, PT/PTT (if indicated)
- x-ray, CT as needed

Treatment
- locate bleeding and achieve hemostasis
1. ABCs
- lean patient forward to minimize swallowing blood and avoid airway obstruction
- apply constant firm pressure for 20 min on cartilaginous part of nose (not bony pyramid)
- if significant bleeding, assess vitals for signs of hemorrhagic shock ± IV NS, cross-match blood

2. Determine Site of Bleeding
- anterior/posterior hemorrhage defined by location in relationship to bony septum
- visualize nasal cavity with speculum
- use cotton pledget with topical lidocaine ± topical decongestant to help identify area of bleeding (often anterior septum)
- if suspicious bleeding disorder, coagulation workup (platelet number and platelet function assay)

3. Control the Bleeding
- first line topical vasoconstrictors
- if first line fails and bleeding adequately visualized, cauterize with silver nitrate
- do not cauterize both sides of the septum at one time due to risk of septal perforation from loss of septal blood supply
A. Anterior hemorrhage treatment
  - if fail to achieve hemostasis with cauterization:
    - place anterior pack* with half inch Vaseline®-soaked ribbon gauze strips layered from nasal floor toward nasal roof extending to posterior choanae or lubricated absorbable packing (i.e. Gelfoam wrapped in Surgicel®) for 2-3 d
    - can also attempt packing with Merocel® or nasal tampons of different shapes
    - can also apply Floseal® (hemostatic matrix consisting of topical human thrombin and cross-linked gelatin) if other methods fail
B. Posterior hemorrhage treatment
  - if unable to visualize bleeding source, then usually posterior source:
    - place posterior pack* using a Foley catheter, gauze pack, or Epistat® balloon
    - subsequently, layer anterior packing bilaterally
    - admit to hospital with packs in for 3-5 d
    - watch for complications: hypoxemia (nasopulmonic reflex), toxic shock syndrome (Rx: remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration
C. If anterior/posterior packs fail to control epistaxis
  - ligation or embolization of culprit arterial supply by interventional radiology
  - ± septoplasty
* antibiotics for any posterior pack or any pack left for >48 h because of risk of toxic shock syndrome

4. Prevention
- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of HTN and coagulopathies

Hoarseness

Definitions
- hoarseness: change in voice quality, ranging from voice harshness to voice weakness; reflects abnormalities anywhere along the vocal tract from oral cavity to lungs
- dysphonia: a general alteration in voice quality
- aphonia: no sound emanates from vocal folds

Acute Laryngitis

Definition
- <2 wk inflammatory changes in laryngeal mucosa

Etiology
- viral: influenza, adenovirus
- bacterial: Group A Streptococcus
- mechanical acute voice strain → submucosal hemorrhage → vocal cord edema → hoarseness
- environmental: toxic fume inhalation

Clinical Features
- URTI symptoms, hoarseness, aphony, cough attacks, ± dyspnea
- true vocal cords erythematous/edematous with vascular injection and normal mobility

Treatment
- usually self-limited, resolves within ~1 wk
- voice rest
- humidification
- hydration

If hoarseness present for >2 wk in a smoker, laryngoscopy must be done to rule out malignancy

Vocal Cord Paralysis

Unilateral: affected cord lies in the parmedian position, inadequate glottic closure during phonation → weak, breathy voice. Usually medializes with time whereby phonation and aspiration improve. Treatment options include voice therapy, injection laryngoplasty (Radiesse), medialization using silastic block

Bilateral: cords rest in midline therefore voice remains good but respiratory function is compromised and may present as stridor. If no respiratory issues, may monitor closely and wait for improvement. If respiratory issues, intubate and will likely require a tracheotomy
• avoid irritants (e.g., smoking)
• treat with antibiotics if there is evidence of coexistent bacterial pharyngitis

**Chronic Laryngitis**

**Definition**
- >2 wk inflammatory changes in laryngeal mucosa

**Etiology**
- repeated attacks of acute laryngitis
- chronic irritants (dust, smoke, chemical fumes)
- chronic voice strain
- chronic rhinosinusitis with postnasal drip
- chronic EtOH use
- esophageal disorders: GERD, Zenker’s diverticulum, hiatus hernia
- systemic: allergy, hypothyroidism, Addison’s disease

**Clinical Features**
- chronic dysphonia: rule out malignancy
- cough, globus sensation, frequent throat clearing 2° to GERD
- laryngoscopy: cords erythematous, thickened with ulceration/granuloma formation, and normal mobility

**Treatment**
- remove offending irritants
- treat related disorders (e.g., antisecretory therapy for GERD)
- speech therapy with voice rest
- ± antibiotics ± steroids to decrease inflammation
- laryngoscopy to rule out malignancy

**Vocal Cord Polyps**

**Definition**
- structural manifestation of vocal cord irritation
- acutely, polyp forms 2° to capillary damage in the subepithelial space during extreme voice exertion

**Etiology**
- most common benign tumor of vocal cords
- voice strain (muscle tension dysphonia)
- laryngeal irritants (GERD, allergies, tobacco)

**Epidemiology**
- 30-50 yr of age
- M>F

**Clinical Features**
- hoarseness, aphonia, cough attacks ± dyspnea
- pedicled or sessile polyp on free edge of vocal cord
- typically polyp asymmetrical, soft, and smooth
- more common on the anterior 1/3 of the vocal cord
- intermittent respiratory distress with large polyps

**Treatment**
- avoid irritants
- endoscopic laryngeal microsurgical removal if persistent or if high risk of malignancy

**Vocal Cord Nodules**

**Definition**
- vocal cord callus
- i.e., “screamer’s or singer’s nodules”

**Etiology**
- early nodules occur 2° to submucosal hemorrhage
- mature nodules result from hyalinization which occurs with long-term voice abuse
- chronic voice strain
- frequent URTI, smoke, EtOH

---

**Vocal Cords: Polyps vs. Nodules**

<table>
<thead>
<tr>
<th>Polyps</th>
<th>Nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral, asymmetric</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Acute onset</td>
<td>Gradual onset</td>
</tr>
<tr>
<td>May resolve spontaneously</td>
<td>Often follow a chronic course</td>
</tr>
<tr>
<td>Subepithelial capillary breakage</td>
<td>Acute: submucosal hemorrhage or edema Chronic: hyalinization within submucosal lesion</td>
</tr>
<tr>
<td>Soft, smooth, fusiform, pedunculated mass</td>
<td>Acute: small, discrete nodules Chronic: hard, white, thickened fibrosed nodules</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>Voice rest but no whispering, hydration, speech therapy if refractory to therapy</td>
</tr>
<tr>
<td>Surgical excision if persistent or in presence of risk factors for laryngeal cancer</td>
<td>Surgical excision as last resort</td>
</tr>
</tbody>
</table>
Epidemiology
- frequently in singers, children, bartenders, and school teachers
- F>M

Clinical Features
- hoarseness worst at end of day
- on laryngoscopy
  - often bilateral
  - at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords – point of maximal cord vibration
- chronic nodules may become fibrotic, hard, and white

Treatment
- voice rest
- hydration
- speech therapy
- avoid irritants
- surgery rarely indicated for refractory nodules

Benign Laryngeal Papillomas

Etiology
- HPV types 6, 11
- possible hormonal influence, possibly acquired during delivery

Epidemiology
- biphasic distribution: 1) birth to puberty (most common laryngeal tumor) and 2) adulthood

Clinical Features
- hoarseness and airway obstruction
- can seed into tracheobronchial tree
- highly resistant to complete removal
- some juvenile papillomas resolve spontaneously at puberty
- may undergo malignant transformation
- laryngoscopy shows wart-like lesions in supraglottic larynx and trachea

Treatment
- microdebridement or CO₂ laser
- adjuvants under investigation: interferon, cidofovir, acyclovir
- HPV vaccine may prevent/decrease the incidence but more research is needed

Laryngeal Carcinoma
- see Neoplasms of the Head and Neck, OT35

Salivary Glands

Sialadenitis

Definition
- inflammation of salivary glands

Etiology
- viral most common (mumps)
- bacterial causes: *S. aureus, S. pneumoniae, H. influenzae*
- obstructive vs. non-obstructive
- obstructive infection involves salivary stasis and bacterial retrograde flow

Predisposing Factors
- HIV
- anorexia/bulimia
- Sjögren’s syndrome
- Cushing’s, hypothyroidism, DM
- hepatic/renal failure
- meds that increase stasis: diuretics, TCAs, β-blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)
Clinical Features
- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- ± fever
- ± leukocytosis
- ± suppurative drainage from punctum of the gland

Investigations
- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

Treatment
- bacterial: treat with cloxacillin ± abscess drainage, sialogogues
- viral: no treatment

Sialolithiasis

Definition
- ductal stone (mainly hydroxyapatite) in adults, sand/sludge in children, leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

Risk Factors
- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, DM, EtOH, hypercalcemia, psychiatric medication)

Clinical Features
- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculus

Investigations
- U/S ± sialogram

Treatment
- may resolve spontaneously
- encourage salivation to clear calculus
- massage, analgesia, antibiotics, sialogogues (e.g. lemon wedges, sour lemon candies), warm compresses
- remove calculi endoscopically, by dilating duct or orifice, or by excision through floor of the mouth
- if calculus is within the gland parenchyma, the whole gland must be excised

Salivary Gland Neoplasms

Etiology
- anatomic distribution
  - parotid gland: 70-85%
  - submandibular gland: 8-15%
  - sublingual gland: 1%
  - minor salivary glands, most concentrated in hard palate: 5-8%
- malignant (see Table 15, OT32 and Table 16, OT36)
- benign
  - benign mixed (pleomorphic adenoma): 80%
  - Warthin's tumor (3-10% bilateral, M>F): 10%
  - cysts, lymph nodes and adenomas: 10%
  - oncocytoma: <1%

Epidemiology
- 3-6% of all head and neck neoplasms in adults
- mean age at presentation: 55-65
- M=F
Parotid Gland Neoplasms

Clinical Features
- 80% benign (pleomorphic adenoma: most common), 20% malignant (mucoepidermoid: most common)
- if bilateral, suggests benign process (Warthin’s tumor, Sjögren’s, bulimia, mumps) or possible lymphoma
- facial nerve involvement (i.e. facial paralysis): increases risk of malignancy

Investigations
- FNA biopsy
- CT, U/S, or MRI to determine extent of tumor

Treatment
- treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
- pleomorphic adenomas are excised due to risk of malignant transformation (5% risk over prolonged period of time)
- superficial tumor
  - superficial parotidectomy above plane of CN VII ± radiation
  - incisional biopsy contraindicated
- deep lesion
  - near-total parotidectomy sparing as much of CN VII as possible
  - if CN VII involved then it is removed and cable grafted
- complications of parotid surgery
  - hematoma, infection, salivary fistula, temporary facial paresis, Frey’s syndrome (gustatory sweating)

Prognosis
- benign: excellent, <5% of pleomorphic adenomas may recur
- malignant: dependent on stage and type of malignancy (see Table 16, OT36)

Neck Masses

Approach to a Neck Mass
- ensure that the neck mass is not a normal neck structure (hyoid, transverse process of C1 vertebra, prominent carotid bulb)
- any neck mass persisting for >2 wk should be investigated for possible neoplastic causes

Table 15. Acquired Causes of Neck Lumps According to Age

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Possible Causes of Neck Lump</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>1. Inflammatory 2. Congenital 3. Neoplastic</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1. Neoplastic 2. Inflammatory 3. Congenital</td>
</tr>
</tbody>
</table>

Differential Diagnosis
- congenital
  - lateral (branchial cleft cyst, lymphatic/venous/venolymphatic malformation)
  - midline (thyroglossal duct cyst, dermoid cyst, laryngocele)
- infectious/inflammatory
  - reactive lymphadenopathy (2º to tonsillitis, pharyngitis)
  - infectious mononucleosis
  - Kawasaki, Kikuchi, Kimura
  - HIV
  - salivary gland calculi, sialadenitis
  - thyroiditis
- granulomatous disease
  - mycobacterial infections
  - sarcoidosis
- neoplastic
  - lymphoma
  - salivary gland tumors
  - thyroid tumors
  - metastatic malignancy ("unknown primary")

Inflammatory vs. Malignant Neck Masses

<table>
<thead>
<tr>
<th>History</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painful</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>HN/inf</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Fever</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Weight loss</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>CA risk factors</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Age Younger</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Rubbery</td>
<td>Y</td>
<td>Ooc.</td>
</tr>
<tr>
<td>Rock hard</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Mobile</td>
<td>Y</td>
<td>± fixed</td>
</tr>
</tbody>
</table>
Evaluation

Investigations
- history and physical (including nasopharynx and larynx)
- all other investigations and imaging are dependent upon clinical suspicion following history and physical
- laboratory investigations
  - WBC: infection vs. lymphoma
  - Mantoux TB test
  - thyroid function tests and scan
- imaging
  - neck U/S
  - CT scan
  - angiography: vascularity and blood supply to mass
- biopsy: for histologic examination
  - FNA: least invasive
  - needle biopsy
  - open biopsy: for lymphoma
- identification of possible primary tumor (rule out a metastatic lymph node from an "unknown primary")
  - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
  - biopsy of normal tissue of nasopharynx, tonsils, base of tongue, and hypopharynx
  - primary identified 95% of time → stage and treat
  - primary occult 5% of time: excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (squamous cell carcinoma)

Congenital Neck Masses

Branchial Cleft Cysts/Fistula

Embryology
- at the 6th wk of development, the 2nd branchial arch grows over the 3rd and 4th arches and fuses with the neighbouring caudal pre-cardial swelling forming the cervical sinus
- 3 types of malformations
  1. branchial fistula: persistent communication between skin and GI tract
  2. branchial sinus: blind-ended tract opening to skin
  3. branchial cyst: persistent cervical sinus with no external opening

Clinical Features
- 2nd branchial cleft malformations most common
  - sinuses and fistulae present in infancy as a small opening anterior to the sternocleidomastoid muscle
  - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following a URTI
- 1st branchial cleft malformations present as sinus/fistula or cyst in preauricular area or on face over angle of mandible
- 3rd branchial cleft malformations present as recurrent thyroiditis or thyroid abscess and have a tract leading usually to the left pyriform sinus
- there is controversy whether or not 4th branchial cleft anomalies exist, as they may be remnants of the thyrothyrmic axis

Treatment
- surgical removal of cyst or fistula tract
- if infected: allow infection to settle before removal (antibiotics may be required)
Figure 19. Branchial cleft cysts

**Thyroglossal Duct Cysts**

**Embryology**
- thyroid originates as ventral midline diverticulum at base of tongue caudal to junction of 3rd and 4th branchial arches (foramen cecum) and migrates down to inferior aspect of neck
- thyroglossal duct cysts are vestigial remnants of tract

**Clinical Features**
- usually presents in childhood or during 20-40s as a midline cyst that enlarges with URTI and elevates with swallowing and tongue protrusion

**Treatment**
- pre-operative antibiotics to reduce inflammation (infection before surgery is a well described cause of recurrence)
- small potential for neoplastic transformation so complete excision of cyst and tissue around tract up to foramen cecum at base of tongue with removal of central portion of hyoid bone (Sistrunk procedure) recommended
**Lymphatic Malformation**

**Definition**
- lymphatic malformation arising from vestigial lymph channels of neck

**Clinical Features**
- usually present by age 2
- can be macrocystic (composed of large thin-walled cysts, usually below level of mylohyoid muscle) or microcystic (composed of minute cysts, usually above level of mylohyoid muscle)
- usually painless, soft, compressible
- infection causes a sudden increase in size

**Treatment**
- can regress spontaneously after bacterial infection, therefore do not plan surgical intervention until several months after infection
- macrocystic lesions can be treated by sclerotherapy or surgical excision
- microcystic lesions are difficult to treat, but can be debulked

**Neoplasms of the Head and Neck**

**Pre-Malignant Disease**
- leukoplakia
  - hyperkeratosis of oral mucosa
  - risk of malignant transformation 5-20%
- erythroplakia
  - red superficial patches adjacent to normal mucosa
  - commonly associated with epithelial dysplasia
  - associated with carcinoma in situ or invasive tumor in 40% of cases
- dysplasia
  - histopathologic presence of mitoses and prominent nucleoli
  - involvement of entire mucosal thickness = carcinoma in situ
  - associated progression to invasive cancer in 15-30% of cases

**Investigations**
- initial metastatic screen includes CXR
- scans of liver, brain, and bone only if clinically indicated
- CT scan is superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI is superior to discriminate tumor from mucus and to detect bone marrow invasion
- ± PET scans

**Treatment**
- treatment depends on
  - histologic grade of tumor
  - stage
  - physical and psychological health of patient
  - facilities available
  - expertise and experience of the medical and surgical oncology team
- in general
  - 1º surgery for malignant oral cavity tumors with radiotherapy reserved for salvage or poor prognostic indicators
  - 1º radiotherapy for nasopharynx, oropharynx, hypopharynx, larynx malignancies with surgery reserved for salvage
  - palliative chemotherapy for metastatic or incurable disease
  - concomitant chemotherapy increases survival in advanced disease
  - chemotherapy has a role as induction therapy prior to surgery and radiation
  - panendoscopy to detect primary disease when lymph node metastasis is identified
  - anti-EGFR treatment (cetuximab, panitumumab) has a role as concurrent therapy with radiation for SCC of the head and neck (for advanced local and regional disease)

**Prognosis**
- synchronous tumors occur in 9-15% of patients
- late development of 2nd primary most common cause of post-treatment failure after 36 mo
<table>
<thead>
<tr>
<th>Etiology</th>
<th>Epidemiology</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Cavity</td>
<td>95% SCC others: sarcoma, melanoma, minor salivary gland tumor</td>
<td>Mean age: 50-60 yr M&gt;F</td>
</tr>
<tr>
<td>Nose and Paranasal Sinus</td>
<td>75-80% SCC Adenocarcinoma (2nd most common) and mucoepidermoid 99% in maxillary/ethmoid sinus 10% arise from minor salivary glands</td>
<td>Mean age: 50-70 yr Rare tumors ↓ incidence in last 5-10 yr</td>
</tr>
<tr>
<td>Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx, and Larynx)</td>
<td>Nasopharynx 90% SCC – 10% lymphoma</td>
<td>Mean age: 50-59 yr M:F = 2.4:1 Incidence 0.8 per 100,000 100x increased incidence in Southern Chinese</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>95% SCC – poorly differentiated</td>
<td>Mean age: 50-70 yr M:F = 4:1</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>95% SCC 3 sites: 1. pyriform sinus (60%) 2. post-cricoid (30%) 3. post pharyngeal wall (10%)</td>
<td>Mean age: 50-70 yr M&gt;F 8-10% of all H&amp;N cancer</td>
</tr>
<tr>
<td>Larynx</td>
<td>SCC most common 3 sites: 1. supraglottic (30-35%) 2. glottic (60-65%) 3. subglottic (1%)</td>
<td>Mean age: 45-75 yr M:F = 10:1 45% of all H&amp;N cancer</td>
</tr>
<tr>
<td>Salivary Gland</td>
<td>40% mucoepidermoid 30% adenoid cystic 5% acinic cell 5% malignant mixed 5% lymphoma</td>
<td>Mean age: 55-65 yr M=F 3-6% of all H&amp;N cancer Rate of malignancy: Parotid 15-25% Submandibular 37-42% Minor salivary &gt;80%</td>
</tr>
<tr>
<td>Thyroid (90% benign – 10% malignant)</td>
<td>&gt;80% papillary 5-15% follicular 5% medullary &lt;5% anaplastic 1-5% Hurthle cell 1-2% metastatic</td>
<td>Mean age: 44-55 yr Rare tumor</td>
</tr>
<tr>
<td>Parathyroid</td>
<td>Mean age: 44-55 yr</td>
<td>Rare tumor</td>
</tr>
</tbody>
</table>
### Table 17. Quick Look-Up Summary of Head and Neck Malignancies – Diagnosis and Treatment

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Cavity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic neck mass (30%)</td>
<td>Biopsy</td>
<td>1º surgery</td>
<td>5 yr survival</td>
</tr>
<tr>
<td>Non-healing ulcer ± bleeding</td>
<td>CT</td>
<td>local resection</td>
<td>T1/T2: 75%</td>
</tr>
<tr>
<td>Dysphagia, sialorrhea, dysphonia</td>
<td></td>
<td>± neck dissection</td>
<td>T3/T4: 30-35%</td>
</tr>
<tr>
<td>Oral fetor, otalgia, leukoplakia, or erythroplakia (pre-malignant changes or CIS)</td>
<td>FNA/CT</td>
<td>± reconstruction</td>
<td>Poor prognostic indicators</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2º radiation</td>
<td>Depth of invasion, close surgical margins location (tongue worse than floor of mouth)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cervical nodes, extra-capsular spread</td>
</tr>
<tr>
<td><strong>Nose and Paranasal Sinus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early symptoms:</td>
<td>CT/MRI</td>
<td>Surgery and radiation</td>
<td>5 yr survival: 30-60%</td>
</tr>
<tr>
<td>Unilateral nasal obstruction</td>
<td>Biopsy</td>
<td>Chemoradiotherapy</td>
<td>Poor prognosis 2º to late presentation</td>
</tr>
<tr>
<td>Epistaxis, rhinorrhea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late symptoms:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2º to invasion of nose, orbit, nerves, oral cavity, skin, skull base, cribiform plate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical nodes (60-90%)</td>
<td>Nasopharyngoscopy</td>
<td>1º radiation, chemoradiation</td>
<td>5 yr survival</td>
</tr>
<tr>
<td>Nasal obstruction, epistaxis</td>
<td>Biopsy</td>
<td>Surgery for limited or recurrent disease</td>
<td>T1: 79%</td>
</tr>
<tr>
<td>Unilateral otitis media ± hearing loss CN III to VI, IX to XII (25%)</td>
<td>CT/MRI</td>
<td></td>
<td>T2: 72%</td>
</tr>
<tr>
<td>Proptosis, voice change, dysphagia</td>
<td></td>
<td></td>
<td>T3: 50-60%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T4: 36-42%</td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odynophagia, otalgia</td>
<td>Biopsy</td>
<td>1º radiation</td>
<td>Base of tongue – control rates</td>
</tr>
<tr>
<td>Ulcerated/enlarged tonsil</td>
<td>CT</td>
<td>2º surgery</td>
<td>T1: &gt;90%, T4: 13-52%</td>
</tr>
<tr>
<td>Fixed tongue/trismus/dysarthria</td>
<td></td>
<td>local resection</td>
<td>Tonsils – cure rate</td>
</tr>
<tr>
<td>Oral fetor, bloody sputum</td>
<td></td>
<td>± neck dissection</td>
<td>T1/T2: 90-100%, T4: 15-33%</td>
</tr>
<tr>
<td>Cervical lymphadenopathy (60%)</td>
<td></td>
<td>± reconstruction</td>
<td>HPV-positive tumors have an approximately 20% improved overall survival rate</td>
</tr>
<tr>
<td>Distant mets: lung/bone/liver (7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypopharynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia, odynophagia</td>
<td>Pharyngoscopy</td>
<td>1º radiation</td>
<td>5 yr survival</td>
</tr>
<tr>
<td>Otalgia, hoarseness</td>
<td>Biopsy</td>
<td>2º surgery</td>
<td>T1: 53%</td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>CT</td>
<td></td>
<td>T2/3: 36-39%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T4: 24%</td>
</tr>
<tr>
<td><strong>Larynx</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odynophagia, odynophagia, globus</td>
<td>Laryngoscopy</td>
<td>1º radiation</td>
<td>5 yr survival</td>
</tr>
<tr>
<td>Otalgia, hoarseness</td>
<td>CT/MRI</td>
<td>2º surgery</td>
<td>T4: &gt;40% (surgery with radiation)</td>
</tr>
<tr>
<td>Dyspnea/stridor</td>
<td></td>
<td>1º surgery for bulky T4 disease</td>
<td>Control rate early lesions &gt;90% (radiation)</td>
</tr>
<tr>
<td>Cough/hemoptysis</td>
<td></td>
<td></td>
<td>10 to 12% of small lesions fail radiotherapy</td>
</tr>
<tr>
<td>Cervical nodes (rare with glottic CA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Salivary Gland</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Painless mass (occ. pain is possible) CN VII palsy</td>
<td>FNA</td>
<td>1º surgery ± neck dissection</td>
<td>Parotid</td>
</tr>
<tr>
<td></td>
<td>MRI/CT/U/S</td>
<td>Post-operative radiotherapy</td>
<td>10 yr survival: 85, 69, 43, and 14% for stages T1 to T4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapy if unresectable</td>
<td>Submandibular</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 yr survival: 82%, 5 yr: 69%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minor salivary gland</td>
</tr>
<tr>
<td>Rapid growth Invasion of skin Constitutional signs/symptoms</td>
<td></td>
<td></td>
<td>10 yr survival: 83, 52, 25, 23% for stages T1 to T4</td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid mass, cervical nodes</td>
<td>FNA</td>
<td>1º surgery</td>
<td>Parcures occur within 5 yr</td>
</tr>
<tr>
<td>Vocal cord paralysis Hyper/hypothyroidism</td>
<td>U/S</td>
<td>I131 for intermediate and high risk well differentiated thyroid cancer</td>
<td>Need long-term follow-up: clinical exam, thyroglobulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parathyroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased serum Ca²⁺</td>
<td>Sestamibi</td>
<td>Wide surgical excision</td>
<td>Recurrence rates</td>
</tr>
<tr>
<td>Neck mass Bone disease, renal disease Pancreatitis</td>
<td></td>
<td>Post-operative monitoring of serum Ca²⁺</td>
<td>1 yr: 27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 yr: 82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 yr: 91%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean survival: 6-7 yr</td>
</tr>
</tbody>
</table>
Thyroid Carcinoma

Table 18. Bethesda Classification of Thyroid Cytology

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic or unsatisfactory</td>
<td>Unknown</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
</tr>
<tr>
<td>Follicular lesion of undetermined significance/</td>
<td></td>
</tr>
<tr>
<td>Adenoma of undetermined significance</td>
<td>5-15%</td>
</tr>
<tr>
<td>Follicular/Hürthle cell neoplasms</td>
<td>15-30%</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60-75%</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
</tr>
</tbody>
</table>

Indications for Post-Operative Radioactive Iodine Ablation – I131
- Adjuvant therapy: decrease recurrent disease
- RAI therapy: treat persistent cancer

Table 19. Thyroid Carcinoma

<table>
<thead>
<tr>
<th>Incidence (% of all thyroid cancers)</th>
<th>Papillary</th>
<th>Follicular</th>
<th>Medullary</th>
<th>Anaplastic</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-75%</td>
<td>10%</td>
<td>3 to 5%</td>
<td></td>
<td>&lt;5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Route of Spread</td>
<td>Lymphatic</td>
<td>Hemogenous</td>
<td>Lymphatic and hemogenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Orphan Annie nuclei, Psammoma bodies, Papillary architecture</td>
<td>Capsular/vascular invasion influences prognosis</td>
<td>Amyloid</td>
<td>May secrete calcitonin, prostaglandins, ACTH, serotonin, kallikrein, or bradykinin</td>
<td>Giant cells, Spindle cells</td>
</tr>
<tr>
<td>Other</td>
<td>Ps – Papillary cancer, Popular (most common), Palpable lymph nodes</td>
<td>Ps – Follicular cancer, Far away mets, Female (3:1), NOT FNA (cannot be diagnosed by FNA)</td>
<td>Ms – Medullary cancer, Multiple endocrine neoplasia (MEN IIa or IIb)</td>
<td>Usually non-Hodgkin’s lymphoma Rapidly enlarging thyroid mass Hx of Hashimoto’s thyroiditis increases risk 60x</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>98% at 10 yr</td>
<td>92% at 10 yr</td>
<td>50% at 10 yr</td>
<td>20-35% at 1 yr</td>
<td>Stage IE 55%-80% Stage IIE 20%-50% Stage IIE/IV 15%-35%</td>
</tr>
<tr>
<td>Treatment</td>
<td>Small tumors: Near total thyroidectomy or lobectomy, Diffuse/bilateral, Total thyroidectomy ± post-operative I131 treatment</td>
<td>Small tumors: Near total thyroidectomy/lobectomy / isthmectomy</td>
<td>Total thyroidectomy</td>
<td>Radiation and chemotherapy, Non-surgical Combined radiation Chemotherapy (CHOP**)</td>
<td></td>
</tr>
</tbody>
</table>

Approach to Thyroid Nodule
- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- any nodule > 5 mm with suspicious sonographic features (particularly microcalcifications) should undergo FNA
- any nodule > 1 cm should undergo FNA
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule

Table 20. Management of the Thyroid Nodule

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioiodine therapy</td>
<td>For the treatment of hyperthyroidism or as adjuvant treatment after surgery in the treatment of papillary or follicular carcinoma</td>
</tr>
<tr>
<td>Chemotherapy and/or radiotherapy</td>
<td>Anaplastic CA or thyroid lymphoma</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Mass that is “suspicious” on FNA</td>
</tr>
<tr>
<td></td>
<td>Malignancy other than anaplastic CA or thyroid lymphoma</td>
</tr>
<tr>
<td></td>
<td>Mass that on FNA is benign but increasing in size on serial imaging and/or &gt; 3-4 cm in size</td>
</tr>
<tr>
<td></td>
<td>Hyperthyroidism not amenable to medical therapy</td>
</tr>
</tbody>
</table>

*U/S findings: cystic: risk of malignancy <1%; solid: risk of malignancy –10%; solid with cystic components: risk of malignancy same as if solid

**CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

*8 symptoms = fever, night sweats, chills, weight loss >10% in 6 mo

**CHOP = cyclophosphamide, adriamycin, vincristine, prednisone
Acute Otitis Media

Definition
- all of: presence of middle ear effusion (MEE); presence of middle ear inflammation (MEI); acute onset of symptoms of MEE and MEI

Epidemiology
- most frequent diagnosis in sick children visiting clinicians’ offices and most common reason for antibiotic administration
- peak incidence between 6-15 mo; ~85% of children have >1 episode by 3 yr old
- seasonal variability: peaks in winter

Etiology
- primary defect causing AOM: Eustachian tube dysfunction/obstruction → stasis/colonization by pathogens
  - bacterial: S. pneumoniae, non-typable H. influenzae, M. catarrhalis, Group A Streptococcus, S. aureus
  - viral: RSV, influenza, parainfluenza, adenovirus
- commonly due to bacterial/viral co-infection

Predisposing Factors
- Eustachian tube dysfunction/obstruction
  - swelling of tubal mucosa
  - upper respiratory tract infection (URTI)
  - allergic rhinitis
  - chronic rhinosinusitis
  - obstruction/infiltration of Eustachian tube ostium
  - tumor: nasopharyngeal carcinoma (adults)
  - adenoid hypertrophy (not due to obstruction but by maintaining a source of infection)
  - barotrauma (sudden changes in air pressure)
  - inadequate tensor palati function: cleft palate (even after repair)
  - abnormal Eustachian tube
  - Down syndrome (horizontal position of Eustachian tube), Crouzon syndrome, cleft palate, and Apert syndrome
- disruption of action of cilia of Eustachian tube: Kartagener’s syndrome
- mucus secreting cells
- capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, cystic fibrosis

Risk Factors
- non-modifiable: young age, family history of OM, prematurity, orofacial abnormalities, immunodeficiencies, Down syndrome, race, and ethnicity
- modifiable: lack of breastfeeding, day care attendance, household crowding, exposure to cigarette smoke and air pollution, pacifier use

Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features
- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers
  - ear-tugging (this alone is not a good indicator of pathology)
  - hearing loss, balance disturbances (rare)
  - irritable, poor sleeping
  - vomiting and diarrhea
  - anorexia
- otoscopy of TM
- hyperemia
- bulging, pus may be seen behind TM
- loss of landmarks: handle and long process of malleus not visible
- RAOM (>3 episodes in 6 mo or >4 in 12 mo)
- At-risk children (permanent hearing loss, speech/language delay, balance problems, poor school performance, ear discomfort, etc)
- Unilateral or bilateral OME with type B tympanogram or persistent effusion > 3 mo
- RADOM (3 episodes in 6 mo or 4 in 12 mo)
- Chronic bilateral OME and documented hearing difficulties > 3 mo
- Unilateral or bilateral OME > 3 mo and symptoms likely attributable to OME (e.g. balance problems, poor school performance, ear discomfort, etc)

Indications for Myringotomy and Tube Placement
- Chronic bilateral OME and documented hearing difficulties > 3 mo
- Unilateral or bilateral OME > 3 mo and symptoms likely attributable to OME (e.g. balance problems, poor school performance, ear discomfort, etc)
- At-risk children (permanent hearing loss, speech/language delay, autism-spectrum disorder, syndromes/craniofacial disorders, blindness, cleft palate, developmental delay) with unilateral or bilateral OME

Clinical Assessment of AOM in Pediatrics
JAMA 2010;304:2161-2169
In assessment of AOM in pediatrics, ear pain is the most useful symptom with a likelihood ratio (LR) of 3.0-7.3. Useful otoscopic signs include redness (LR 8.4, 95% CI 7-11), cloudy (LR 3.0-7.3). Useful otoscopic signs include redness (LR 8.4, 95% CI 7-11), cloudy (LR 3.0-7.3), granular (LR 4.0, 95% CI 3-5), bullous myringitis (LR 5.0, 95% CI 3-7), and perforation (LR 10.0, 95% CI 6-15). Useful signs include tympanic membrane bulging (LR 4.0, 95% CI 3-5), tympanic membrane erythema (LR 4.0, 95% CI 3-5), and tympanic membrane retraction (LR 3.0, 95% CI 2-4).

Conclusion
- The role of antibiotics is largely restricted to pain control at 2-7 d, but must (62%) settle without antibiotics. This can also be achieved by analgesics. However, antibiotic treatment can reduce risk of TM perforation and contralateral AOM episodes. These benefits must be weighed against risks of adverse events from antibiotics.

Main Outcomes:
1) Pain at 24 h, 2-3 d, and 4-7 d; 2) Abnormal tympanometry findings; 3) TM perforation; 4) Contralateral otitis; 5) AOM recurrences; 6) Serious complications from AOM; 7) Adverse effects from antibiotics.

Results: Treatment with antibiotics had no significant impact on pain at 24 h. However, pain at 2-3 d and 4-7 d was lower in the antibiotic groups with a NNT of 20. Antibiotics had no significant effect on tympanometry findings, number of AOM recurrences, or severity of complications. Antibiotic treatment led to a significant reduction in TM perforations (NNT 33) and halved contralateral AOM (NNT 11). Adverse events (vomiting, diarrhea, or rash) occurred more often in children taking antibiotics.

Clinical notes:
- In assessment of age >3 mo, ear pain is the most useful symptom with a likelihood ratio (LR) of 3.0-7.3. Useful otoscopic signs include erythematous (LR 8.4, 95% CI 7-11), cloudy (LR 3.0-7.3), bullous myringitis (LR 5.0, 95% CI 3-7), and perforation (LR 10.0, 95% CI 6-15). Useful signs include tympanic membrane bulging (LR 4.0, 95% CI 3-5), tympanic membrane erythema (LR 4.0, 95% CI 3-5), and tympanic membrane retraction (LR 3.0, 95% CI 2-4).
Diagnosis
• history
  ▪ acute onset of otalgia or ear tugging in a preverbal child, otorrhea, decreased hearing
  ▪ unexplained irritability, fever, upper respiratory symptoms, poor sleeping, anorexia, N/V, and diarrhea
• physical
  ▪ febrile
  ▪ MEE on otoscopy: immobile tympanic membrane, acute otorrhea, loss of bony landmarks, opacification of TM, air-fluid level behind TM
  ▪ MEI on otoscopy: bulging TM with marked discoloration (hemorrhagic, red, gray, or yellow)

Management
• observation for 48-72 h without antimicrobials may be appropriate since >80% of AOM in children resolve spontaneously
• criteria for watchful waiting approach
  ▪ child is >6 mo old
  ▪ child does not have immunodeficiency, chronic cardiac or pulmonary disease, anatomical abnormalities of the head or neck, a history of complicated otitis media (suppurative complications of chronic perforation) or Down syndrome
  ▪ the illness is not severe: otalgia appears to be mild and fever is <102.2°F in the absence of antipyretics
  ▪ parents are capable of recognizing signs of worsening illness and can readily access medical care if the child does not improve
• antimicrobials are indicated if child does not meet the criteria for watchful waiting or does not improve/worsens during observation
• maintain hydration
• symptomatic relief: acetaminophen, ibuprofen
• referral to otolaryngology for myringotomy and tympanostomy tubes may be warranted for recurrent infections

Treatment
• antimicrobial agents for AOM
  ▪ 1st line treatment (no penicillin allergy)
    ▪ amoxicillin: 75 mg/kg/d to 90 mg/kg/d divided 3x/d
  ▪ 2nd line treatment
    ▪ cefprozil: 30 mg/kg/d divided 2x/d
    ▪ cefuroxime axetil: 30 mg/kg/d divided 2x/d
    ▪ ceftriaxone: 50 mg/kg intramuscularly (or intravenously) x 1 dose
    ▪ azithromycin: 10 mg/kg OD x 1 dose, then 5 mg/kg OD x 4 doses
    ▪ clarithromycin: 15 mg/kg/d divided 2x/d
  ▪ if initial therapy fails (i.e. no symptomatic improvement after 2-3 d)
    ▪ amoxicillin-clavulanate: 90 mg/kg/d amoxicillin, 6.4 mg/kg/d clavulanate divided 2x/d for 10 d
  ▪ if AOM-related symptoms do not resolve with amoxicillin/clavulanate, a course of ceftriaxone 50 mg/kg/d intramuscularly (or intravenously) 1/d x 3 doses could be considered

Complications
• extracranial
  ▪ hearing loss and speech delay (secondary to persistent MEE), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction, persistent effusion (often leading to hearing loss)
• intracranial
  ▪ meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis, facial nerve paralysis
• other
  ▪ mastoiditis, labyrinthitis, sigmoid sinus thrombophlebitis

Otitis Media with Effusion

Definition
• presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology
• most common cause of pediatric hearing loss
• not exclusively a pediatric disease
• follows AOM frequently in children
• middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10%
Risk Factors
• same as AOM

Clinical Features
• conductive hearing loss ± tinnitus
  ▪ confirm with audiogram and tympanogram (flat) (see Figure 16B, OT10 and Figure 17B, OT11)
• fullness – blocked ear
• ± pain, low grade fever
• otoscopy of tympanic membrane:
  ▪ discoloration – amber or dull gray with "glue" ear
  ▪ meniscus fluid level behind TM
  ▪ air bubbles
  ▪ retraction pockets/TM atelectasis
• most reliable finding with pneumotoscopy is immobility

Treatment
• expectant: 90% resolve by 3 mo
• document hearing loss with audiogram
• no clinical evidence that antihistamines, decongestants, or antibiotics clear disease faster
• surgery: myringotomy ± ventilation tubes ± adenoidectomy (if enlarged or on insertion of second set of tubes after first set falls out)
• ventilation tubes to equalize pressure and drain ear

Complications of Otitis Media with Effusion
• hearing loss, speech delay, learning problems in young children
• chronic mastoiditis
• ossicular erosion
• cholesteatoma especially when retraction pockets involve pars flaccida
• retraction of tympanic membrane, atelectasis, ossicular fixation

Adenoid Hypertrophy

- size peaks at age 5 and resolves by age 12
- increase in size with repeated URTI and allergies

Clinical Features
• nasal obstruction
  ▪ adenoid facies (open mouth, high arched palate, narrow midface, malocclusion)
  ▪ history of hypernasal voice and snoring
  ▪ long-term mouth breather; minimal air escape through nose
• choanal obstruction
  ▪ chronic rhinosinusitis/rhinitis
  ▪ obstructive sleep apnea
• chronic inflammation
  ▪ nasal discharge, post-nasal drip, and cough
  ▪ cervical lymphadenopathy

Diagnosis
• enlarged adenoids on nasopharyngeal exam (usually with flexible nasopharyngoscope)
• enlarged adenoid shadow on lateral soft tissue x-ray

Complications
• Eustachian tube obstruction leading to serous otitis media
• interference with nasal breathing, necessitating mouth-breathing
• malocclusion
• sleep apnea/respiratory disturbance
• orofacial developmental abnormalities

Adenoidectomy

Indications for Adenoidectomy
• chronic upper airway obstruction with sleep disturbance/apnea ± cor pulmonale
• chronic nasopharyngitis resistant to medical treatment
• chronic serous otitis media and chronic suppurative otitis media (with 2nd set of tubes)
• recurrent acute otitis media resistant to antibiotics
• suspicion of nasopharyngeal malignancy
• persistent rhinorrhea secondary to nasal obstruction

Figure 20. Waldeyer’s ring
An interrupted circle of protective lymphoid tissue at the upper ends of the respiratory and alimentary tracts
Contraindications
- uncontrollable coagulopathy
- recent pharyngeal infection
- conditions that predispose to velopharyngeal insufficiency (cleft palate, impaired palatal function, or enlarged pharynx)

Complications
- bleeding, infection
- velopharyngeal insufficiency (hypernasal voice or nasal regurgitation)
- scarring of Eustachian tube orifice

Sleep-Disordered Breathing in Children

Definition
- spectrum of sleep-related breathing abnormalities ranging from snoring to OSA

Epidemiology
- peak incidence between 2-8 yr when tonsils and adenoids are the largest relative to the pharyngeal airway

Etiology
- due to a combination of anatomic and neuromuscular factors
  - adenotonsillar hypertrophy
  - craniofacial abnormalities
  - neuromuscular hypotonia (i.e. cerebral palsy, Down syndrome)
  - obesity

Clinical Features
- heavy snoring, mouth breathing, pauses or apnea, enuresis, excessive daytime sleepiness, behavioral/learning problems, diagnosis of ADHD, morning headache, failure to thrive

Investigations
- flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
- polysomnography (apnea-hypopnea index >1/h considered abnormal)

Treatment
- surgical: bilateral tonsillectomy and adenoidectomy
- nonsurgical: CPAP, BiPAP, sleep hygiene

Acute Tonsillitis

see Pediatrics, P59

Peritonsillar Abscess (Quinsy)

Definition
- cellulitis of space behind tonsillar capsule extending onto soft palate leading to abscess

Etiology
- bacterial: Group A strep (GAS) (50% of cases), S. pyogenes, S. aureus, H. influenzae, and anaerobes

Epidemiology
- can develop from acute tonsillitis with infection spreading into plane of tonsillar bed
- unilateral
- most common in 15-30 yr age group

Clinical Features
- fever and dehydration
- sore throat, dysphagia, and odynophagia
- extensive peritonsillar swelling but tonsil may appear normal
- edema of soft palate
- uvular deviation
- trismus (due to irritation and reflex spasm of the medial pterygoid)
- dysphonia (edema → failure to elevate palate) 2º to CN X involvement
- unilateral referred otalgia
- cervical lymphadenitis
Complications
- aspiration pneumonia ñ to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

Treatment
- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 d if cultures positive for GAS
- add PO/IV metronidazole or clindamycin x 10 d if culture positive for Bacteroides
- consider tonsillectomy after second episode

Other Sources of Parapharyngeal Space Infections
- pharyngitis
- acute suppurative parotitis (see Salivary Glands, OT30)
- AOM
- mastoiditis (Bezold's abscess)
- odontogenic infection

Tonsillectomy

Absolute Indications:
- most common indication: sleep-disordered breathing
- 2nd most common indication: recurrent throat infections
- tonsillar hypertrophy causing upper airway obstruction, obstructive sleep apnea, severe dysphagia, or cardiopulmonary complications such as cor pulmonale
- suspicion of malignancy (e.g. lymphoma, squamous cell carcinoma)
- orofacial/dental deformity
- hemorrhagic tonsillitis

Relative Indications (To Reduce Disease Burden):
- recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 yr, or at least 3 episodes per year for 3 yr, with documentation in the medical record for each episode of sore throat and 1 or more of the following: temperature >38.3°C, cervical adenopathy, tonsillar exudate, or positive test for Group A ß-hemolytic streptococcus (Paradise Criteria)
- chronic tonsillitis with halitosis (bad breath) or sore throat ± tonsilloliths (clusters of calcified material that form in the crevices of the tonsils)
- complications of tonsillitis: quinsy/peritonsillar abscess, parapharyngeal abscess, retropharyngeal abscess
- failure to thrive

Relative Contraindications:
- velopharyngeal insufficiency: overt or submucous/covert cleft of palate, impaired palatal function due to neurological or neuro-muscular abnormalities
- hematologic: coagulopathy, anemia
- infectious: active local infection without urgent obstructive symptoms

Complications
- hemorrhage: early – within 24 h; delayed – 7-10 d
- odynophagia and/or otalgia; dehydration 2º to odynophagia
- infection
- atlantoaxial subluxation (Grisel's syndrome): rare

Airway Problems in Children

Differential Diagnosis by Age Group

Neonates (Obligate Nose Breeders)
- extralaryngeal
  - choanal atresia (e.g. CHARGE syndrome)
  - nasopharyngeal dermoid, glioma, encephalocele
  - glossoptosis: Pierre-Robin sequence, Down syndrome, lymphatic malformation, hemangioma
- laryngeal
  - laryngomalacia: most common cause of stridor in children
  - laryngocele
• vocal cord palsy (due to trauma or Arnold-Chiari malformation)
  • glottic web
  • subglottic stenosis
  • laryngeal cleft
  • tracheal
    • tracheoesophageal fistula
    • tracheomalacia
    • vascular rings

2-3 Months
• congenital
  • laryngomalacia
  • vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
  • laryngeal papilloma
• acquired
  • subglottic stenosis: post-intubation
  • tracheal granulation: post-intubation
  • tracheomalacia: post-tracheotomy and TEF repair

Infants – Sudden Onset
• foreign body aspiration
• croup
• bacterial tracheitis
• caustic ingestion
• epiglottitis

Children and Adults
• infection
  • Ludwig’s angina
  • peritonsillar/parapharyngeal abscess
  • retropharyngeal abscess
• neoplastic
  • squamous cell carcinoma (SCC) (adults): larynx, hypopharynx
  • retropharyngeal: lymphoma, neuroblastoma
  • nasopharyngeal: carcinoma, rhabdomyosarcoma
• allergic
  • angioneurotic edema
  • polyps (suspect cystic fibrosis in children)
• trauma
  • laryngeal fracture, facial fracture
  • burns and lacerations
  • post-intubation
  • caustic ingestion
• congenital
  • lingual thyroid/tonsil

Signs of Airway Obstruction

Stridor
• note quality, timing (inspiratory or expiratory)
• body position important
  • lying prone: subglottic hemangioma, double aortic arch
  • lying supine: laryngomalacia, glossoptosis
• site of stenosis
  • vocal cords or above: inspiratory stridor
  • subglottis and extrathoracic trachea: biphasic stridor
  • distal tracheobronchial tree: expiratory stridor

Respiratory Distress
• nasal flaring
• supraclavicular and intercostal indrawing
• sternal retractions
• use of accessory muscles of respiration
• tachypnea
• cyanosis
• altered LOC
Feeding Difficulty and Aspiration
- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- laryngeal cleft → aspiration pneumonia

Acute Laryngotracheobronchitis (Croup)
- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining and associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

Etiology
- viral: parainfluenzae I (most common), II, III, influenza A and B, RSV

Clinical Features
- age: 4 mo-5 yr
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea-lion bark)
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- “steeple-sign” on AP x-ray of neck
- if recurrent croup, think subglottic stenosis

Treatment
- racemic epinephrine via MDI q1-2h, prn (only if in respiratory distress)
- systemic corticosteroids (e.g. dexamethasone, prednisone)
- adequate hydration
- close observation for 3-4 h
- intubation if severe
- hospitalize if poor response to steroids after 4 h and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)
- if recurrent episodes of croup-like symptoms, consider bronchoscopy several weeks after acute episode settles to rule out underlying subglottic stenosis

Acute Epiglottitis
- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

Etiology
- H. influenzae type b
- relatively uncommon condition due to Hib vaccine

Clinical Features
- any age, most commonly 1-4 yr
- rapid onset
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up (“tripod” posture), open mouth, drooling, tongue protruding, sore throat, dysphagia

Investigations and Management
- investigations and physical exam may lead to complete obstruction, thus preparations for intubation or tracheotomy must be made prior to any manipulation
- stat ENT/anesthesia consult(s)
- WBC (elevated), blood and pharyngeal cultures after intubation
- lateral neck radiograph (only done if patient stable)

Treatment
- secure airway
- IV access with hydration
- antibiotics: IV cefuroxime, cefotaxime, or ceftriaxone
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis
Subglottic Stenosis

Congenital
- diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage)

Acquired
- following prolonged, repeated, or traumatic intubation
  - most commonly due to endotracheal intubation; nasal intubation is less traumatic and preferred in long-term intubation as it puts less pressure on the subglottis (tube sits at different orientation) and there is less movement
  - subglottic stenosis is related to duration of intubation and pressure of the endotracheal tube cuff
- can also be due to foreign body, infection (e.g. TB, diphtheria, syphilis), or chemical irritation

Clinical Features
- biphasic stridor
- respiratory distress
- recurrent/prolonged croup

Diagnosis
- rigid laryngoscopy and bronchoscopy

Treatment
- if soft stenosis: divide tissue with knife or laser, dilate with balloon ± steroids
- if firm stenosis: laryngotracheoplasty

Laryngomalacia

- short aryepiglottic folds, omega-shaped epiglottis, pendulous mucosa
- caused by indrawing of supraglottis on inspiration leading to laryngopharyngeal reflux of acid

Clinical Features
- high-pitched inspiratory stridor at 1-2 wk
- constant or intermittent and more pronounced supine and following URTI
- usually mild but when severe can be associated with cyanosis or feeding difficulties, leading to failure to thrive

Treatment
- observation is usually sufficient as symptoms spontaneously subside by 12-18 mo in >90% of cases
- if severe, division of the aryepiglottic folds (supraglottoplasty) provides relief

Foreign Body

Ingested
- usually stuck at cricopharyngeus
- coins, toys, batteries (emergency)
- presents with drooling, dysphagia, stridor if very large

Aspirated
- usually stuck at right mainstem bronchus
- peanuts, carrot, apple core, popcorn, balloons
- presentation
  - stridor if lodged in trachea
  - unilateral “asthma” if bronchial, therefore often misdiagnosed as asthma
  - if totally occludes airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax, death

Diagnosis and Treatment
- any patient with suspected foreign body should be kept NPO immediately
- inspiration-expiration chest x-ray (if patient is stable)
- bronchoscopy or esophagoscopy with removal
- rapid onset, not necessarily febrile or elevated WBC
Deep Neck Space Infection

- most commonly arise from an infection of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
- often a rapid onset and may progress to fatal complications

**Etiology**
- usually mixed aerobes and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes

**Clinical Features**
- sore throat or pain and trismus
- dysphagia and odynophagia
- stridor and dyspnea
- late findings may include dysphonia and hoarseness
- swelling of the face and neck, erythema
- asymmetry of the oropharynx with purulent oral discharge
- lymphadenopathy

**Diagnosis**
- lateral cervical view plain radiograph
- CT
- MRI

**Treatment**
- secure the airway
- surgical drainage
- maximum doses of IV systemic antimicrobials regimens according to the site of infection

### Common Medications

**Table 21. Antibiotics**

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin (Amoxil®)</td>
<td>Adult: 500 mg PO tid Children: 75-90 mg/kg/d in 2 divided doses</td>
<td>Streptococcus, Pneumococcus, H. influenzae, Proteus coverage</td>
<td>May cause rash in patients with infectious mononucleosis</td>
</tr>
<tr>
<td>piperacillin with tazobactam (Zosyn®)</td>
<td>3 g PO q6h</td>
<td>Gram-positive and negative aerobes and anaerobes plus Pseudomonas coverage</td>
<td>May cause pseudomembranous colitis</td>
</tr>
<tr>
<td>ciprofloxacin (Cipro®, Ciloxan®)</td>
<td>500 mg PO bid</td>
<td>Pseudomonas, Streptococci, MRSA, and most Gram-negative; no anaerobic coverage</td>
<td>Do not give systemic quinolones to children</td>
</tr>
<tr>
<td>erythromycin (Erythrocin®, EryPed®, Staticin®, T-Stat®)</td>
<td>500 mg PO qid</td>
<td>Alternative to penicillin</td>
<td>Ototoxic</td>
</tr>
</tbody>
</table>

**Table 22. Otic Drops**

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciprofloxacin (Ciprodex®)</td>
<td>4 gtt in affected ear bid</td>
<td>For otitis externa and complications of otitis media Pseudomonas, Streptococci, MRSA, and most Gram-negative; no anaerobic coverage</td>
<td></td>
</tr>
<tr>
<td>neomycin, polymyxin B sulfate, and hydrocortisone (Cortisporin®)</td>
<td>5 gtt in affected ear tid</td>
<td>For otitis externa Used for inflammatory conditions which are currently infected or at risk of bacterial infections</td>
<td>May cause hearing loss if placed in inner ear</td>
</tr>
<tr>
<td>hydrocortisone and acetic acid (VoSoL HC®)</td>
<td>5-10 gtt in affected ear tid</td>
<td>For otitis media Bactericidal by lowering pH</td>
<td></td>
</tr>
<tr>
<td>tobramycin and dexamethasone (TobraDex®)</td>
<td>5-10 gtt in affected ear bid</td>
<td>For chronic suppurative otitis media</td>
<td>Risk of vestibular or cochlear toxicity</td>
</tr>
</tbody>
</table>
Table 23. Nasal Sprays

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluornolide (Nasalade®)</td>
<td>Allergic rhinitis</td>
<td>Requires up to 4 wk of consistent use to have effect</td>
</tr>
<tr>
<td>budesonide (Rhinocort®)</td>
<td>Chronic sinusitis</td>
<td>Long-term use</td>
</tr>
<tr>
<td>beclometasone (Beconase®)</td>
<td></td>
<td>Dries nasal mucosa; may cause minor bleeding</td>
</tr>
<tr>
<td>mometasone furoate, monohydrate (Nasonex®)</td>
<td></td>
<td>Patient should stop if epistaxis</td>
</tr>
<tr>
<td>fluticasone furoate (Veramyst®)</td>
<td></td>
<td>May sting</td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>levocabastine (Livostin®)</td>
<td>Allergic rhinitis</td>
<td>Immediate effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If no effect by 3 d then discontinue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use during allergy season</td>
</tr>
<tr>
<td>Decongestant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxymetazoline (Visine L.R.®) phenylephrine</td>
<td>Acute sinusitis</td>
<td>Careful if patient has HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-term use (&lt;5 d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If long-term use, can cause decongestant addiction (i.e. rhinitis medicamentosa)</td>
</tr>
<tr>
<td>Antibiotic/Decongestant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gramicidin</td>
<td>Acute sinusitis</td>
<td></td>
</tr>
<tr>
<td>Anticholinergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipratropium bromide (Atrovent®)</td>
<td>Vasomotor rhinitis</td>
<td>Careful not to spray into eyes as can cause burning or precipitation of narrow angle glaucoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased rate of epistaxis when combined with topical nasal steroids</td>
</tr>
<tr>
<td>Lubricants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>saline, Polysporin®, Vaseline®</td>
<td>Dry nasal mucosa</td>
<td>Use pm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhinase® and Secaris® may cause stinging</td>
</tr>
</tbody>
</table>

Source: Dr. MM Carr

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Furman JM, Cass SP. Benign parotid parannosal vesicle. NEJM 1999;341:1580-1586.


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Table 1. Average Vitals at Various Ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Pulse (bpm)</th>
<th>Respiration Rate (br/min)</th>
<th>sBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>90-170</td>
<td>40-60</td>
<td>70-90</td>
</tr>
<tr>
<td>3-12 mo</td>
<td>80-165</td>
<td>30-55</td>
<td>80-100</td>
</tr>
<tr>
<td>1-2 yr</td>
<td>80-125</td>
<td>25-45</td>
<td>90-100</td>
</tr>
<tr>
<td>3-11 yr</td>
<td>70-115</td>
<td>18-30</td>
<td>100-110</td>
</tr>
<tr>
<td>12-15 yr</td>
<td>60-100</td>
<td>12-18</td>
<td>110-130</td>
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<td>15 mo</td>
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<td>16 mo</td>
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<tr>
<td>4-6 yr</td>
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<tr>
<td>16-18 yr</td>
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<tr>
<td>Every autumn</td>
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</tbody>
</table>

Primary Care

Visit Overview

- schedule:
  - newborn (within 1 wk post-discharge), 1, 2, 4, 6, 9, 12, 15, 18, 24 mo
  - annually between age 2 to 6; every other year between age 6 to 11
- content:
  - history and physical exam including growth, development, and nutrition
  - routine immunizations
  - counseling and anticipatory guidance

Routine Immunization

Table 2. U.S. Recommended Immunization Schedule 0-18 Years Old (2014)

<table>
<thead>
<tr>
<th>Age</th>
<th>DTaP (IM)</th>
<th>Td (IM)</th>
<th>IPV (IM)</th>
<th>PCV-13 (IM)</th>
<th>Rot-1 (PO)</th>
<th>Men-C (IM)</th>
<th>Men-C (IM)</th>
<th>Men-C (IM)</th>
<th>MMR (SC)</th>
<th>Var (SC)</th>
<th>MMR (SC)</th>
<th>Men-C (IM)</th>
<th>HbA1c (IM)</th>
<th>HepB (IM)</th>
<th>HPV (IM)</th>
<th>HepA (IM)</th>
<th>Inf (IM)</th>
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<tbody>
<tr>
<td>Birth</td>
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<td>14-16 yr</td>
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</tr>
<tr>
<td>Every autumn</td>
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<td>✓</td>
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</tr>
</tbody>
</table>

IM = intramuscular; PO = per oral; SC = subcutaneous; “*starting at 6 mo of age,” “**2 dose series (second dose given 6-18 mo after first)”
Table 2. U.S. Recommended Immunization Schedule 0-18 Years Old (2014) (continued)

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Adverse Reaction</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP-IPV</td>
<td>Prolonged crying</td>
<td>Evolving unstable neurologic disease</td>
</tr>
<tr>
<td></td>
<td>Hypotonic unresponsive state (rare)</td>
<td>Hypotensive/hypotonic following previous vaccine</td>
</tr>
<tr>
<td></td>
<td>Seizure on day of vaccine (rare)</td>
<td>Anaphylactic reaction to neomycin or streptomycin</td>
</tr>
<tr>
<td>Rot-1</td>
<td>Cough</td>
<td>History of intussusception</td>
</tr>
<tr>
<td></td>
<td>Diarrhea, vomiting</td>
<td>Immuneuncompromised Abdominal disorder (e.g. Meckel’s diverticulum)</td>
</tr>
<tr>
<td></td>
<td>Especially painful injection</td>
<td>Received blood products (e.g. immunoglobulin) within 42 d</td>
</tr>
<tr>
<td>MMR</td>
<td>Measle-like rash (7-14 d)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy, arthralgia, arthritis</td>
<td>Immunocompromised infants (except healthy HIV positive children)</td>
</tr>
<tr>
<td></td>
<td>Parotitis (rare)</td>
<td>Anaphylactic reaction to gelatin</td>
</tr>
<tr>
<td></td>
<td>Especially painful injection</td>
<td></td>
</tr>
<tr>
<td>Var</td>
<td>Mild varicella-like papules or vesicles</td>
<td>Pregnancy or planning to get pregnant within 3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaphylactic reaction to gelatin</td>
</tr>
<tr>
<td>HepB</td>
<td>Mild varicella-like papules or vesicles</td>
<td>Anaphylactic reaction to Baker’s yeast</td>
</tr>
<tr>
<td>MMRV</td>
<td>Same as MMR and Var vaccines</td>
<td>Same as MMR and Var vaccines</td>
</tr>
<tr>
<td>dTAP</td>
<td>Malaise, myalgia</td>
<td>1st trimester pregnancy</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Inf</td>
<td>Hypersensitivity reaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>HPV-4</td>
<td>Pruritis</td>
<td></td>
</tr>
</tbody>
</table>

dTAP = diphtheria, tetanus, acellular pertussis vaccine; DTaP-IPV = diphtheria, tetanus, acellular pertussis, inactivated polio vaccine (i.e. Pentacel®, Pentavax®); HPV-4 = human papillomavirus vaccine; Inf = influenza vaccine; MMR = measles, mumps, rubella vaccine; Men-C-C = meningococcal c conjugate vaccine; MMRV = measles, mumps, rubella, varicella vaccine; Pneu-C-13 = pneumococcal 13-valent conjugate vaccine; Rot-1 = rotavirus oral vaccine; Var = varicella vaccine

Vaccine Administration

- injection site
  - infants (<12 mo): anterolateral thigh
  - children: deltoid, subcutaneous tissue of the upper triceps area of the arm (IM injections should be given at 90° angle; SC injections should be given at 45° angle)

- timing of injection
  - varicella and MMR vaccines can be given at either the same visit or separated by >4 wk (MMRV at 4-6 yr)
  - HPV vaccine given in 3 doses to all adolescents aged 11-12 yr old (HPV-2 or HPV-4 for females; only HPV-4 for males) (0, 2, 6 mo)

Growth and Development

Growth

- growth is not linear
- most rapid growth during first two years and at puberty
- tissues grow at different times
  - first two years = CNS; mid-childhood = lymphoid tissue; puberty = gonads
- measurement of growth
  - premature infants (<37 wk) use corrected GA until age 2 yr
  - body proportion = upper/lower segment ratio (use symphysis pubis as midpoint)
    - newborn = 1.7, adult male = 0.9, adult female = 1.0
Average Growth Parameters

Table 3. Parameter of Average Growth at Birth

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Growth</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>3.25 kg (7 lbs)</td>
<td>Gain 20-30 g/d (term neonate)</td>
<td>Weight loss (up to 10% of birth weight) in first 7 d of life is normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 x birth wt by 4-5 mo</td>
<td>Neonate should regain birth weight by ~10-14 d of age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 x birth wt by 1 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4 x birth wt by 2 yr</td>
<td></td>
</tr>
<tr>
<td>Length/Height</td>
<td>50 cm (20 in)</td>
<td>25 cm in 1st yr</td>
<td>Measure supine length until 2 yr of age, then measure standing height</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12 cm in 2nd yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 cm in 3rd yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4-7 cm/yr until puberty</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/2 adult height at 2 yr</td>
<td></td>
</tr>
<tr>
<td>Head Circumference</td>
<td>35 cm (14 in)</td>
<td>2 cm/mo for 1st 3 mo</td>
<td>Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 cm/mo at 3-6 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.5 cm/mo at 6-12 mo</td>
<td></td>
</tr>
</tbody>
</table>

Reflexes

Table 4. Reflexes

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Maneuver to Elicit Reflex</th>
<th>Appropriate Reflex Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moro</td>
<td>Infant placed semi-upright, head supported by examiner’s hand, sudden withdrawal of supported head with immediate return of support</td>
<td>Abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms</td>
</tr>
<tr>
<td>Galant</td>
<td>Infant held in ventral suspension and one side of back is stroked along paravertebral line</td>
<td>Pelvis will move in the direction of stimulated side</td>
</tr>
<tr>
<td>Grasp</td>
<td>Placement of examiner’s finger in infant’s palm</td>
<td>Flexion of infant’s fingers</td>
</tr>
<tr>
<td>ATNR</td>
<td>Turn infant’s head to one side</td>
<td>“Fencing” posture (extension of ipsilateral leg and arm and flexion of contralateral arm)</td>
</tr>
<tr>
<td>Placing</td>
<td>Dorsal surface of infant’s foot placed touching edge of table</td>
<td>Flexion followed by extension of ipsilateral limb up onto table (resembles primitive walking)</td>
</tr>
<tr>
<td>Rooting</td>
<td>Tactile stimulus near mouth</td>
<td>Infants pursue stimulus with face</td>
</tr>
<tr>
<td>Parachute</td>
<td>Tilt infant to side while in sitting position</td>
<td>Ipsilateral arm extension, present by 6-8 mo</td>
</tr>
</tbody>
</table>

ATNR = asymmetric tonic neck reflex

Developmental Milestones

Table 5. Developmental Milestones

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>Turns head side to side when supine</td>
<td>Hands fist, thumb in fist</td>
<td>Cries, startles to loud noises</td>
<td>Calms when comforted</td>
</tr>
<tr>
<td>2 mo</td>
<td>Briefly raises head when prone, holds head erect when upright</td>
<td>Pulls at clothes</td>
<td>Variety of sounds (e.g. coos, gurgles)</td>
<td>Smiles responsively, recognizes and calms down to familiar voice, follows movement with eyes</td>
</tr>
<tr>
<td>4 mo</td>
<td>Lifts head and chest when prone, holds head steady when supported sitting, rolls prone to supine</td>
<td>Briefly holds object when placed in hand, reaches for midline objects</td>
<td>Turns head towards sounds</td>
<td>Laughs responsively, follows moving toy or person with eyes, responds to people with excitement (e.g. leg movement)</td>
</tr>
<tr>
<td>6 mo</td>
<td>Tripod sit, pivots in prone position</td>
<td>Ulnar or raking grasp, transfers objects from hand to hand, brings objects to mouth</td>
<td>Babbles</td>
<td>Stranger anxiety, beginning of object permanence</td>
</tr>
<tr>
<td>9 mo</td>
<td>Sits well without support, crawls, pulls to stand, stands with support</td>
<td>Early pincer grasp with straight wrist</td>
<td>“Mama, dada” – appropriate, imitates 1 word, responds to “no” regardless of tone</td>
<td>Plays games (e.g. peek-a-boo), reaches to be picked up</td>
</tr>
<tr>
<td>12 mo</td>
<td>Gets into sitting position without help, stands without support, walks while holding on</td>
<td>Neat pincer grasp, releases ball with throw</td>
<td>2 words, follows 1-step command, uses facial expression, sounds, actions to make needs known</td>
<td>Responds to own name, separation anxiety begins</td>
</tr>
</tbody>
</table>

*Use corrected GA until 2 yr

Scoliosis Screening

Despite mass school screening implemented in parts of the USA and Canada in the 1970s-90s, the Canadian (1994) and American (2004) Task Forces on Preventive Health Care do NOT currently recommend routine screening using the Forward Bend Test (FBT). Cohort studies indicate that the Forward Bend Test has poor sensitivity for identifying pathological curves. Furthermore, there is no evidence to suggest that screening and increased bracing lead to better outcomes.

Abnormal Reflex Response

- Absence may suggest CNS abnormality
- Persistence after 4-6 mo may indicate abnormality (e.g. cerebral palsy)
- Asymmetry suggests focal motor lesions (e.g. brachial plexus injury)
- Upgoing plantar reflex (Babinski’s sign) normal in infants up to age 2 yr
### Table 5. Developmental Milestones (continued)

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mo</td>
<td>Walks without support, crawls up stairs/steps</td>
<td>Picks up and eats finger foods, scribbles, stacks 2 blocks</td>
<td>Says 4-5 words, points to needs/wants</td>
<td>Looks to see how others react (e.g. after falling)</td>
</tr>
<tr>
<td>18 mo</td>
<td>Runs, walks forward pulling toys or carrying objects</td>
<td>Tower of 3 cubes, scribbling, eats with spoon</td>
<td>10 words, follows simple commands</td>
<td>Shows affection towards others, points to show interest in something</td>
</tr>
<tr>
<td>24 mo</td>
<td>Climbs up 2 feet per step, runs, kicks ball, walks up and down stairs</td>
<td>Tower of 6 cubes, undresses</td>
<td>2-3 word phrases, uses &quot;I, me, you&quot;, 50% intelligible, understands 2-step commands</td>
<td>Parallel play, helps to dress</td>
</tr>
<tr>
<td>3 yr</td>
<td>Tricycle, climbs up 1 foot per step, down 2 feet per step, stands on one foot briefly</td>
<td>Copies a circle, turns pages one at a time, puts on shoes, dress/undress fully except buttons</td>
<td>Combines 3 or more words into sentence, recognizes colors, prepositions, plurals, counts to 10, 75% intelligible</td>
<td>Knows sex and age, shares some of the time, plays make-believe games</td>
</tr>
<tr>
<td>4 yr</td>
<td>Hops on 1 foot, down 1 foot per step</td>
<td>Copies a cross, uses scissors, buttons clothes</td>
<td>Speech 100% intelligible, uses past tense, understands 3-part directions</td>
<td>Cooperative play, fully toilet-trained by day, tries to comfort someone who is upset</td>
</tr>
<tr>
<td>5 yr</td>
<td>Skips, rides bicycle</td>
<td>Copies a triangle and square, prints name, ties shoelaces</td>
<td>Fluent speech, future tense, alphabet, retells sequence of a story</td>
<td>Cooperates with adult requests most of the time, separates easily from caregiver</td>
</tr>
</tbody>
</table>

*Use corrected GA until 2 yr

### Nutrition

#### Dietary Requirements

<table>
<thead>
<tr>
<th>Weight</th>
<th>&lt;10 kg</th>
<th>10-20 kg</th>
<th>&gt;20 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Needs</td>
<td>100 kcal/kg/d</td>
<td>1,000 cal + 50 kcal/kg/d for each kg &gt;10</td>
<td>1,500 cal + 20 kcal/kg/d for each kg &gt;20</td>
</tr>
</tbody>
</table>

#### Dietary Recommendations

- **0-6 mo:** breast milk or formula
  - exclusive breast milk during first 6 mo recommended over formula unless contraindicated
  - breastfed infants require supplements: vitamin K (all babies get at birth, breastfed or not), vitamin D (400-800 IU/d), fluoride (after 6 mo if not sufficient in water), iron (6-12 mo, only if not receiving fortified cereals/meat/meat alternatives)
- **>6 mo:** solid food introduction – do not delay beyond 9 mo
  - 2-3 new foods per week with a few days in between each food to allow time for adverse reaction identification
  - suggested order of introduction
    - meat, meat alternatives, and iron-enriched cereal (rice cereal is least allergenic)
    - pureed vegetables
    - fruit
- **9-12 mo:** finger foods and switch to homogenized (3%) milk
  - foods to avoid
    - honey until past 12 mo (risk of botulism)
    - added sugar, salt
    - excessive milk (i.e. no more than 16 oz/d after 1 yr)
    - juice (not nutritious, too much sugar)
    - anything that is a choking hazard (chunks, round foods like grapes)

#### Breastfeeding

- content of breast milk
  - colostrum (first few days): clear, rich in nutrients (i.e. high protein, low fat), immunoglobulin
  - mature milk: 70:30 whey-casein ratio, fat from dietary butterfat, carbohydrate from lactose
- advantages
  - easily digested, low renal solute load
  - immunologic
    - contains IgA, macrophages, active lymphocytes, lysoenzymes, lactoferrin (which inhibits *E. coli* growth in intestine)
    - lower pH promotes growth of lactobacillus in GI tract
  - parent-child bonding
  - economical, convenient
Injury Prevention Counseling

- injuries are the leading cause of death in children >1 yr of age
- main causes: motor vehicle accidents, burns, drowning, falls, choking, infanticide

Table 7. Injury Prevention Counseling

<table>
<thead>
<tr>
<th>Age 0-6 mo</th>
<th>Age 6-12 mo</th>
<th>Age 1-2 yr</th>
<th>Age 2-5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not leave alone on bed, on changing table, or in tub</td>
<td>Install stair barriers</td>
<td>Never leave unattended</td>
<td>Bicycle helmet</td>
</tr>
<tr>
<td>Keep crib rails up</td>
<td>Discourage use of walkers</td>
<td>Keep pot handles turned to back of stove</td>
<td>Never leave unsupervised at home, driveway, or pool</td>
</tr>
<tr>
<td>Check water temperature before bathing</td>
<td>Avoid play areas with sharp-edged tables and corners</td>
<td>Caution with whole grapes, nuts, raw carrots, hotdog, etc. due to choking hazard</td>
<td>Teach bike safety, stranger safety, and street safety</td>
</tr>
<tr>
<td>Do not hold hot liquid and infant at the same time</td>
<td>Cover electrical outlets</td>
<td>No running while eating</td>
<td>Swimming lessons (&gt;4 yr)</td>
</tr>
<tr>
<td>Check milk temperature before feeding</td>
<td>Unplug appliances when not in use</td>
<td>Appropriate car seats</td>
<td>Fences around pools</td>
</tr>
<tr>
<td>Appropriate car seats are required before leaving hospital</td>
<td>Keep small objects, plastic bags, cleaning products, and medications out of reach</td>
<td>Supervise during feeding</td>
<td>Appropriate car seats (toddler seat)</td>
</tr>
</tbody>
</table>

Note: This list is not exhaustive. For more details, see Rourke Baby Record (http://www.rourkebabyrecord.ca/pdf/RBR2011Ort_Eng.pdf)
Common Complaints

Breath Holding Spells

- epidemiology: 0.1-5% of healthy children 6 mo–4 yr of age, usually start during first year of life
- etiology: child is provoked (usually by anger, injury, or fear) → holds breath and becomes silent → spontaneously resolves or loses consciousness
- types
  - cyanotic (more common), usually associated with anger/frustration
  - pallid, usually associated with pain/surprise
- management
  - usually resolves spontaneously and rarely progresses to seizure
  - help child control response to frustration and avoid drawing attention to spell

Circumcision

- elective procedure
  - recent evidence shows health benefits outweigh risks and justify access to procedure
  - often for religious or culture reasons
- benefits: prevention of phimosis and slightly reduced incidence of UTI, STD, balanitis, cancer of the penis
- complications (<1%): local infection, bleeding, urethral injury
- contraindications: presence of genital abnormalities (e.g. hypospadias) or known bleeding disorder

Crying/Fussing Child

- history
  - description of baseline feeding, sleeping, crying patterns
  - infectious symptoms: fever, tachypnea, rhinorrhea, ill contacts
  - feeding intolerance: gastroesophageal reflux with esophagitis, N/V, diarrhea, constipation
  - trauma
  - recent immunizations (vaccine reaction) or medications (drug reactions), including maternal drugs taken during pregnancy (neonatal withdrawal syndrome) and drugs that may be transferred via breast milk
  - inconsistent history, pattern of numerous emergency department visits, high-risk social situations all raise concern of maltreatment

Table 8. Physical Exam and Differential Diagnosis

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Possible Examination Findings</th>
<th>Possible Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEENT</td>
<td>Bulging fontanelle</td>
<td>Meningitis, shaken baby syndrome, hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Blepharospasm, tearing</td>
<td>Corneal abrasion, glaucoma</td>
</tr>
<tr>
<td></td>
<td>Retinal hemorrhage</td>
<td>Shaken baby syndrome</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal infections</td>
<td>Thrush, gingivostomatitis, herpangina, otitis media</td>
</tr>
<tr>
<td>Neurological</td>
<td>Irritability or lethargy</td>
<td>Meningitis, shaken baby syndrome</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Poor perfusion</td>
<td>Sepsis, anomalous coronary artery, meningitis, myocarditis, CHF</td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea</td>
<td>Pneumonia, CHF, Respiratory disease, response to pain</td>
</tr>
<tr>
<td>Grunting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>Mass, empty RLQ</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Scrotal swelling</td>
<td>Incarcerated hernia, testicular torsion</td>
</tr>
<tr>
<td></td>
<td>Penile/clitoral swelling</td>
<td>Hypospadias, testicular torsion</td>
</tr>
<tr>
<td>Rectal</td>
<td>Anal fissure</td>
<td>Constipation or diarrhea</td>
</tr>
<tr>
<td></td>
<td>Hemoccult positive stool</td>
<td>Intussusception, NEC, volvulus</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Point tenderness or decreased movement</td>
<td>Fracture, syphilis, osteomyelitis, toe/finger hair tourniquet</td>
</tr>
</tbody>
</table>
Infantile Colic

• definition: unexplained paroxysms of irritability and crying for >3 h/d, >3 d/wk for >3 wk in an otherwise healthy, well-fed baby (rule of 3s)
• epidemiology: 10% of infants; usual onset 10 d to 3 mo of age with peak at 6-8 wk
• etiology: lag in development of normal peristaltic movement in gastrointestinal tract; other theories suggest a lack of self-soothing mechanisms or extreme of normal
• management
  ▪ parental relief, rest, and reassurance
  ▪ hold baby, pacifier, car ride, music, vacuum, check diaper
  ▪ medications (Ovol® drops, gripe water) have no proven benefit, some evidence for probiotics
  ▪ if breastfeeding, elimination of cow's milk protein from mother's diet (effective in very small percentage of cases)
  ▪ try casein hydrolysate formula (Nutramigen®)
  ▪ time – all resolve, most in the first 2-3 mo of life

Dentition and Caries

Dentition
• primary dentition (20 teeth)
  ▪ first tooth at 5-9 mo (lower incisor), then 1/mo
  ▪ 6-8 central teeth by 1 yr
  ▪ assessment by dentist 6 mo after eruption of first tooth and certainly by 1 yr of age (Grade B recommendation)
• secondary dentition (32 teeth)
  ▪ first adult tooth is 1st molar at 6 yr, then lower incisors

Caries
• milk caries: decay of superior front teeth and back molars in first 4 yr of life
• cause: often due to prolonged feeding (e.g. put to bed with bottle, prolonged breastfeeding)
• prevention
  ▪ no bottle at bedtime, clean teeth after last feed
  ▪ minimize juice and sweetened pacifier
  ▪ clean teeth with soft damp cloth or toothbrush and water
  ▪ water fluoridation

Enuresis

Definition
• involuntary urinary incontinence by day and/or night in child >5 yr

General Approach
• should be evaluated if dysuria, change in color, odor, stream, secondary or diurnal, change in gait, stoo incontinence

Primary Nocturnal Enuresis
• definition: involuntary loss of urine at night, bladder control has never been attained
• epidemiology: M>F; 10% of 6 yr olds, 3% of 12 yr olds, 1% of 18 yr olds
• etiology: developmental disorder or maturational lag in bladder control while asleep
• management
  ▪ time and reassurance (~20% resolve spontaneously each yr)
  ▪ behavior modification (limiting fluids, voiding prior to sleep), bladder retention exercises, scheduled toileting overnight has limited effectiveness
  ▪ conditioning: "wet" alarm wakes child upon voiding (70% success rate)
  ▪ medications (considered second line therapy, may be used for sleepovers/camp): DDAVP oral tablets (high relapse rate, costly), imipramine (Tofranil®) (rarely used, lethal if overdose, cholinergic side effects)

Secondary Enuresis
• definition: involuntary loss of urine at night, develops after child has sustained period of bladder control (>6 mo)
• etiology: inorganic regression due to stress or anxiety (e.g. birth of sibling, significant loss, family discord), focused on other activities, secondary to organic disease (UTI, DM, DI, neurogenic bladder, CP, seizures, pinworms)
• management: treat underlying cause
Diurnal Enuresis
- **definition:** daytime wetting (60-80% also wet at night)
- etiology: micturition deferral (holding urine until last minute) due to psychosocial stressor (e.g. shy), structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders, DM
- management: treat underlying cause, behavioral (scheduled toileting, double voiding, good bowel program), pharmacotherapy

Encopresis
- **definition:** fecal incontinence in a child >4 yr old, at least once per mo for 3 mo
- prevalence: 1-1.5% of school-aged children (rare in adolescence); M:F = 6:1 in school-aged children
- causes: chronic constipation (retentive encopresis), Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, anorectal malformations, bowel obstruction

Retentive Encopresis
- **definition:** child holds bowel movement, develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
- etiology
  - physical: painful stooling often secondary to constipation
  - emotional: disturbed parent-child relationship, coercive toilet training, social stressors
- clinical presentation
  - history
    - crosses legs or stands on toes to resist urge to defecate
    - distressed by symptoms, soiling of clothes
    - toilet training coercive or lacking in motivation
    - may show oppositional behavior
    - abdominal pain
  - physical exam
    - digital rectal exam: large fecal mass in rectal vault
    - anal fissures (result from passage of hard stools)
    - palpable stool in LLQ
- management
  - complete clean-out of bowel: PEG 3350 given orally is most effective, enemas and suppositories may be second line therapies, but these are invasive and often less effective
  - maintenance of regular bowel movements (see Pediatric Gastroenterology, Constipation Treatment, P38)
  - assessment and guidance regarding psychosocial stressors
  - behavioral modification
- complications: recurrence, toxic megacolon (requires >3-12 mo to treat), bowel perforation

Toilet Training
- 90% of children attain bladder control before bowel control
- generally, females train earlier than males
- 25% by 2 yr (in North America), 98% by 3 yr have daytime bladder control
- signs of toilet readiness
  - ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several hours (large enough bladder), can recognize need to go, able to remove clothing

Failure to Thrive
- definition
  - weight <3rd percentile, falls across two major percentile curves, or <80% of expected weight for height and age
  - inadequate caloric intake most common factor in poor weight gain
  - may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
  - factors affecting physical growth: genetics, intrauterine factors, internal time clock, nutrition, endocrine hormones, chronic infections/diseases, psychosocial factors
- clinical presentation
  - history
    - nutritional intake
    - current symptoms
    - past illnesses

**Energy Requirements**
- 0-10 kg: 100 kcal/kg/d
- 10-20 kg: 1,000 kcal + 50 kcal/kg/d for each kg >10
- > 20 kg: 1,500 kcal + 20 kcal/kg/d for each kg >20
• family history: growth, puberty, parental height and weight including mid-parental height
• psychosocial history
• physical exam
  • growth parameters, plotted: height, weight, head circumference, arm span
  • vital signs
  • complete head to toe exam
  • dysmorphic features or evidence of chronic disease
  • upper to lower segment ratio
  • sexual maturity staging
  • signs of maltreatment or neglect
• investigations (as indicated by clinical presentation)
  • CBC, blood smear, electrolytes, T4, TSH
  • bone age x-ray
  • chromosomes/karyotype
  • chronic illness: chest (CXR, sweat Cl-), cardiac (CXR, ECG, Echo), GI (celiac screen, inflammatory markers, malabsorption), renal (urinalysis), liver (enzymes, albumin)

Table 9. Failure to Thrive Patterns

<table>
<thead>
<tr>
<th>Growth Parameters</th>
<th>Suggestive Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Wt</td>
<td>Normal Ht</td>
</tr>
<tr>
<td></td>
<td>Normal HC</td>
</tr>
<tr>
<td></td>
<td>Caloric insufficiency</td>
</tr>
<tr>
<td></td>
<td>Decreased intake</td>
</tr>
<tr>
<td></td>
<td>Hypermetabolic state</td>
</tr>
<tr>
<td></td>
<td>Increased losses</td>
</tr>
<tr>
<td>Decreased Wt</td>
<td>Decreased Ht</td>
</tr>
<tr>
<td></td>
<td>Normal HC</td>
</tr>
<tr>
<td></td>
<td>Structural dystrophies</td>
</tr>
<tr>
<td></td>
<td>Constitutional growth delay (BA &lt; CA)</td>
</tr>
<tr>
<td>Decreased Wt</td>
<td>Decreased Ht</td>
</tr>
<tr>
<td></td>
<td>Decreased HC</td>
</tr>
<tr>
<td></td>
<td>Intrauterine insult</td>
</tr>
<tr>
<td></td>
<td>Genetic abnormality</td>
</tr>
</tbody>
</table>

BA = bone age; CA = chronological age; HC = head circumference; Ht = height; Wt = weight

Non-Organic FTT (90%)
• most common cause of FTT
• results from complex factors in parent-child relationship
  • dietary intake, knowledge about feeding, improper mixing of formula, economic factors
  • feeding environment
  • parent-child interaction, attachment
  • child behaviors, hunger/satiety cues
  • social factors: stress, poverty
  • management
    • most as outpatient using multidisciplinary approach: primary care physician, dietitian, psychologist, social work, Child Protection Services
    • medical: oromotor problems, iron-deficiency anemia, gastroesophageal reflux
    • nutritional: educate about age-appropriate foods, calorie boosting, mealt ime schedules and environment to reach goal of 90-110% IBW, correct nutritional deficiencies, and promote catch-up growth/development
    • behavioral: positive reinforcement, mealt ime environment

Organic FTT (10%)
• inadequate intake: vomiting, oromotor dysfunction, anorexia
• excessive consumption: CHD, CF, hyperthyroidism
• abnormal utilization: inborn errors of metabolism
• excessive output: IBD, celiac, malabsorption
• management: treat specific cause

Energy Requirements
• see Nutrition, P6

Obesity

• definition: BMI >95th percentile for age and height
• risk factors: genetic predisposition (e.g. both parents obese – 80% chance of obese child)
• etiology: organic causes are rare (<5%), but may include Prader-Willi, Carpenter, Turner, Cushing syndromes, hypothyroidism
• complications: association with HTN, dyslipidemia, slipped capital femoral epiphysis, type 2 DM, asthma, obstructive sleep apnea, gynecomastia, polycystic ovarian disease, early menarche, irregular menses, psychological trauma (e.g. bullying, decreased self-esteem, unhealthy coping mechanisms, depression)
• childhood obesity is not reliable predictor of adult obesity unless >180% of IBW; adolescent obesity good predictor of adult obesity
• management
  • encouragement and reassurance; engagement of entire family
- diet: qualitative changes (do not encourage weight loss, but allow for linear growth to catch up with weight), special diets used by adults and very low calorie diets are not encouraged
- behavior modification: increase activity, change eating habits/meal patterns
- education: multidisciplinary approach, dietitian, counseling
- surgery and pharmacotherapy are not frequently used in children
- increase activity, reduce screen time

### Poison Prevention

- keep all types of medicines, vitamins, and chemicals locked up in a secure container
- potentially dangerous: medications, illicit drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- keep alcoholic beverages out of reach: 3 oz hard liquor can kill a 2 yr old
- always read labels before administering medicine to ensure correct medication drug and dose and/or speak with a pharmacist or healthcare provider

### Rashes

#### Table 10. Common Pediatric Rashes

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Differential</th>
<th>Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaper Dermatitis</td>
<td>Irritant contact dermatitis</td>
<td>Shiny, red macules/patches, no skin fold involvement</td>
<td>Eliminate direct skin contact with urine and feces, allow periods of rest without a diaper, frequent diaper changes, topical barriers (petrolatum, zinc oxide or paste), short-term low-potency topical corticosteroids (severe cases)</td>
</tr>
<tr>
<td></td>
<td>Seborrheic dermatitis</td>
<td>Yellow, greasy macules/plaques on erythema, scales</td>
<td>Short-term, low-potency topical corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Candidal dermatitis</td>
<td>Erythematous macerated papules/plaques, satellite lesions, involvement of skin folds</td>
<td>Antifungal agents</td>
</tr>
</tbody>
</table>

#### Other Dermatitis

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis</td>
<td>Erythematous, papules/plaques, oozing, excoriation, lichenification, classic areas of involvement</td>
<td>Eliminate exacerbating factors, maintain skin hydration, corticosteroids, topical calcineurin inhibitor, daily baths</td>
</tr>
<tr>
<td>Nummular dermatitis</td>
<td>Annular erythematous plaques, oozing, crusting</td>
<td>Avoid irritant if identified, potent topical steroid in emollient base, short-term systemic steroids ± antibiotics (severe)</td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>Red papules/plaques vesicles/bullae, only in area of allergen</td>
<td>Mild: soothing lotion (e.g. calamine lotion) Moderate: low-to-intermediate potency topical corticosteroids Severe: systemic corticosteroids and antihistamine</td>
</tr>
<tr>
<td>Irritant contact dermatitis</td>
<td>Morphology depends on irritant</td>
<td>Avoid skin contact</td>
</tr>
<tr>
<td>Dyshidrotic dermatitis</td>
<td>Papulovesicular, cracking/tissuring, hands and feet (“tapioca pudding”)</td>
<td>Mild/moderate: medium/potent topical corticosteroids Severe: systemic corticosteroids, local PUVA or UVA treatments</td>
</tr>
</tbody>
</table>

#### Infectious

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scabies</td>
<td>Polymorphic (red excoriated papules/nodules, burrows), in web spaces/folds, very pruritic</td>
<td>Permethrin (Nix) 5% cream for patient and family (2 applications, 1 wk apart)</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Honey-colored crusts or superficial bullae</td>
<td>Oral antibiotics (e.g. cephalexin/erythromycin) Topical if mild: fucidic acid or mupirocin cream</td>
</tr>
<tr>
<td>Tinea corporis</td>
<td>Round erythematous plaques, central clearing and scaly border</td>
<td>Topical anti-fungal for skin, systemic anti-fungals for nails/head</td>
</tr>
</tbody>
</table>

### Pediatric Exanthems

(see *Infectious Pediatric Exanthems*, P57)

### Drug Reactions

(see *Dermatology*, D21)

### Acne

(see *Dermatology*, D11)
Sleep Disturbances

Types of Sleep Disturbances

• Insufficient sleep quantity
  • Difficulty falling asleep (e.g. limit setting sleep disorder)
  • Preschool and older children
  • Bedtime resistance
  • Due to caregiver's inability to set consistent bedtime rules and routines
  • Often exacerbated by child's oppositional behaviors

• Poor sleep quality
  • Frequent arousals (e.g. sleep-onset association disorder)
  • Infants and toddlers
  • Child learns to fall asleep only under certain conditions or associations (e.g. with parent, held, rocked or fed, with light on, in front of television), and loses ability to self-soothe
  • During the normal brief arousal periods of sleep (q90-120 min), child cannot fall back asleep because same conditions are not present

• Obstructive sleep apnea
  • Epidemiology: 1-5% of preschool aged children, more common in African American children
  • Definition: partial or intermittent complete airway obstruction during sleep causing disrupted ventilation and sleep pattern
  • Features: snoring/gasping/noisy breathing during sleep and irritable/tired/hyperactive during the day
  • Sequelae: cardiovascular (HTN/LV remodeling due to sympathetic activation), growth, cognitive, and behavioral deficits
  • Risk factors: adenotonsillar hypertrophy, obesity
  • Management: watchful waiting, weight reduction, airway pressure devices, or surgery depending on the cause
  • Adenotonsillectomy does not improve executive function or attention but reduces symptoms and improves behavior, quality of life, and polysomnographic findings

• Parasomnias
  • Episodic nocturnal behaviors (e.g. sleepwalking, sleep terrors, nightmares)
  • Often involves cognitive disorientation and autonomic/skeletal muscle disturbance

Management of Sleep Disturbances

• Set strict bedtimes and "wind-down" routines
• Do not send child to bed hungry
• Positive reinforcement for: limit setting sleep disorder
• Always sleep in own bed, in a dark, quiet, and comfortable room
• Do not use bedroom for timeouts
• Systematic ignoring and gradual extinction for: sleep-onset association disorder

Nightmares

• Epidemiology: common in boys, 4-7 yr
• Associated with REM sleep (anytime during night)
• Features: upon awakening, child is alert and clearly recalls frightening dream ± associated with daytime stress/anxiety
• Management: reassurance

Night Terrors

• Epidemiology: 15% of children have occasional episodes
• Abrupt sitting up, eyes open, screaming
• Clinical features: occurs in early hours of sleep, stage 4 of sleep; signs of panic and autonomic arousal, no memory of event, inconsolable, stress/anxiety can aggravate them
• Course: remits spontaneously at puberty
• Management: reassurance for parents, ensure child is safe (e.g. if sleepwalks)

Sudden Infant Death Syndrome

Definition

• Sudden and unexpected death of an infant <12 mo of age in which the cause of death cannot be found by history, examination, or a thorough postmortem and death scene investigation

Epidemiology

• 0.5/1,000 (leading cause of death between 1-12 mo of age); M:F = 3:2
• More common in children placed in prone position
• In full term infants, peak incidence is 2-4 mo; 95% of cases occur by 6 mo
• Increase in deaths during peak RSV season
• Most deaths occur between midnight and 8 AM
Risk Factors
• prematurity, smoking in household, socially disadvantaged, higher incidence in Aboriginals and African Americans
• risk of SIDS is increased 3-5x in siblings of infants who have died of SIDS
• bedsharing: sleeping on a sofa, sleeping with an infant after consumption of alcohol/street drugs or extreme fatigue, infant sleeping with someone other than primary caregiver

Prevention
• “Back to Sleep, Front to Play” (place infant on back when sleeping)
• allow supervised play time daily in prone position (“tummy time”)
• alarms, monitors not recommended – increase anxiety, do not prevent life-threatening events
• avoid overheating and overdressing
• appropriate infant bedding (e.g. firm mattress; avoid loose bedding, pillows, stuffed animals, and crib bumper pads)
• no smoking
• pacifiers appear to have a protective effect; do not reinsert if it falls out during sleep

Child Abuse and Neglect

Definition
• an act of commission (physical, sexual, or psychological abuse) or omission (neglect) by a caregiver that harms a child

Legal Duty to Report
• upon reasonable grounds to suspect abuse and/or neglect, physicians are required by legislation to contact the Child Protective Services (CPS) to personally disclose all information relevant to the child safety concern
• duty to report overrides patient confidentiality; physician is protected against liability

Ongoing Duty to Report
• if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the CPS must be made

Risk Factors
• environmental factors: social isolation, poverty, domestic violence
• caregiver factors: personal history of abuse, psychiatric illness, substance abuse, single parent family, poor social and vocational skills, below average intelligence
• child factors: difficult temperament, disability, special needs (e.g. developmental delay), premature

Physical Abuse

History
• history that is not compatible with physical findings, or history not reproducible
• delay in seeking medical attention that is unexplained by other factors

Physical Exam
• physical findings not explained by underlying medical condition
• growth parameters (weight, height, head circumference)
• recurrent or multiple injuries not explained by accidental injury or child’s development level
• patterned skin injuries: belt buckle, hand prints, burns that do not match provided history
• injury location: bruises on areas with abundant soft-tissue cushioning, such as abdomen, buttocks, genitalia, fleshy part of cheek; bruises on ears; posterior rib/metaphyseal/scapular/vertebral/sternal fractures (more suspicious for non-accidental injuries); immersion burns (e.g. hot water)
• altered mental status: head injury, poisoning

Investigations
• document all injuries on a body diagram: type, location, size, shape, color, pattern
• photography of skin injuries is ideal (police or hospital photography preferred; do not use physician’s personal camera)
• blood tests to rule out medical causes (e.g. thrombocytopenia or coagulopathy)
• screen for abdominal trauma (transaminases and amylase): if increased, abdo CT recommended
• skeletal survey in children <2 yr
• bone scan can be beneficial for assessing rib fractures (not helpful for skull or metaphyseal region due to active bone growth) – consider bone scan if equivocal findings on initial skeletal survey
• dilated eye examination by pediatric ophthalmologist to rule out retinal hemorrhage
• be aware of “red herrings” (e.g. Mongolian blue spots vs. bruises)
• neuroimaging: CT and/or MRI

Apparent Life-Threatening Events
A group of conditions often marked by an episode of apnea, cyanosis, change in tone, or change in mental status occurring in a child, where an observer fears the child may be dying. There is no clear connection between most ALTEs and SIDS. Evaluating for a cause of the ALTE (e.g. infection, cardiac, neurologic) is guided by history, physical exam, and period of observation

Presentation of Neglect
• FTT, developmental delay
• Inadequate or dirty clothing, poor hygiene
• Child exhibits poor attachment to parents, no stranger anxiety
Sexual Abuse

Epidemiology
• peak ages at 2-6 yr and 12-16 yr
• most perpetrators are male and known to child
  ▪ in decreasing order: family member, non-relative known to victim, stranger

History
• diagnosis usually depends on child disclosing to someone or forensic interview done by a trained individual
• psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of trust, low self-esteem, school failure, sexually aggressive behavior, advanced sexual knowledge, sexual preoccupation or play

Physical Exam
• recurrent UTIs, pregnancy, STDs, vaginitis, vaginal bleeding, pain, genital injury, enuresis

Investigations
• depend on presentation, age, sex, and pubertal development of child
  ▪ sexual assault examination kit within 24 h if prepubertal, within 72 h if pubertal
  ▪ rule out STD, UTI, pregnancy (consider STD prophylaxis or emergency contraception)
  ▪ rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)

Neglect

History
• from child and each caregiver separately (if possible)

Physical Exam
• head to toe (do not force), growth parameters, nutrition status
• dental care
• emotional state

Investigations
• blood tests to rule out medical conditions (e.g. thrombocytopenia or coagulopathy)

Management of Physical Abuse, Child Abuse, and Neglect
• report all suspicions to CPS; request emergency visit if imminent risk to child or any siblings in the home
• acute medical care: hospitalize for medical evaluation or treatment of injuries if indicated
• arrange consultation to social work and appropriate follow-up
• may need to discharge child directly to CPS or to responsible guardian under CPS supervision

Adolescent Medicine

Adolescent History (HEEADSSS)
• tailor your history according to the clinical context

Home: Who do you live with? What kind of place do you live in?

Education/Employment: What grade are you in? What are your favorite subjects? What was your average on your last report card?

Eating: Tell me about your meals/snacks in a typical day. Have you ever gone on a diet?  
(for Eating Disorders – see Psychiatry, PS26)

Activities: What do you do after school? On the weekends? How much time do you spend on the computer/watching TV every day? Do you use social media (i.e. Facebook, Twitter, Instagram, etc.)?

Drugs: Which seems to be more popular at your school, alcohol or drugs? How often do you drink/smoke marijuana/take other drugs? Do you smoke cigarettes? When you drink, do you usually get drunk? Have you ever passed out or not been able to remember what happened while you were drinking? Has anything bad ever happened to you while you were drunk or stoned?  
(for Substance Abuse – see Psychiatry, PS18)

Sexuality: Are you romantically interested in anyone? When you think about having sex with someone, do you think about girls, boys, or both? Have you ever had sex with anyone? Whether the answer is yes or no, the next question is: What activities would you include in the term ‘having sex’? What do you do to prevent getting a STD/getting pregnant/getting someone pregnant? Has anyone ever given you money, drugs, or other stuff in exchange for sex?  
(for Sexually Transmitted Diseases – see Gynecology, GY25)
Suicidality/Depression: On a scale of 1 to 10, where 1 is so sad that you might kill yourself and 10 is the happiest you could be, where are you most days? Is there a difference between school days and the weekend? Have you ever thought seriously about suicide? Did you make a plan? (for Depression/Suicide – see Psychiatry, PS7, PS2)

Safety/Violence: Do you ever get into a car with a driver who has been drinking? Do you always wear a seatbelt/bicycle helmet? Are you being bullied at school? Has anyone ever touched you in an unwanted way?

For Normal and Abnormal Pubertal Development, P31

Cardiology

Congenital Heart Disease

PRENATAL CIRCULATION

- Embryologic Development
  - most critical period of fetal heart development is between 3-8 wk gestation
  - single heart tube grows rapidly, forcing it to bend back upon itself and assume the shape of a four chambered heart; insults at this time are most likely to lead to CHD

- Before Birth
  - fetal lungs are bypassed by flow through fetal shunts
    - shunting deoxygenated blood
      - ductus arteriosus: connection between pulmonary artery and aorta
    - shunting oxygenated blood
      - foramen ovale: connection between right and left atria
      - ductus venosus: connection between umbilical vein and inferior vena cava

- At Birth
  - with first breath, lungs open up → pulmonary resistance decreases → pulmonic blood flow increases
  - separation of low resistance placenta → systemic circulation becomes a high resistance system → ductus venosus closure
  - increased pulmonary flow → increased left atrial pressures → foramen ovale closure
  - increased oxygen concentration in blood after first breath → decreased prostaglandins → ductus arteriosus closure
  - closure of fetal shunts and changes in vascular resistance → infant circulation assumes normal adult flow

Prevalence of depression: 1-2% in pre-pubertal children and 6-8% in adolescents

Date rape comprises 80% of sexual assault in teenagers

Fetal circulation is designed so that oxygenated blood is preferentially delivered to the brain and myocardium

Figure 1. Prenatal circulation
Epidemiology
- 8/1,000 live births have CHD, which may present as a heart murmur, heart failure, or cyanosis; VSD is the most common lesion

Investigations
- Echo, ECG, CXR
- pre and postductal oxygen saturations, 4 limb BPs, hyperoxia test

CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE
- cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 30 g/dL
- acyanotic heart disease (i.e. L to R shunt, obstruction occurring beyond lungs): blood passes through pulmonic circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis
- cyanotic heart disease (i.e. R to L shunt): blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis

Atrial Septal Defect
- 3 types: ostium primum (common in DS), ostium secundum (most common type, 50-70%), sinus venosus (defect located at entry of superior vena cava into right atrium)
- epidemiology: 6-8% of congenital heart lesions
- natural history
  - 80-100% spontaneous closure rate if ASD diameter <8 mm
  - if remains patent, CHF and pulmonary HTN can develop in adult life
- clinical presentation
  - history: often asymptomatic in childhood
  - physical exam: grade 2-3/6 pulmonic outflow murmur, widely split and fixed S2
  - children with large ASDs may have signs of heart failure (tachypnea, FTT, hepatomegaly, pulmonary rales/retractions)
- investigations
  - ECG: RAD, mild RVH, RBBB
  - CXR: increased pulmonary vasculature, cardiac enlargement
  - Echo: test of choice
- management: elective surgical or catheter closure between 2-5 yr of age

Ventricular Septal Defect
- most common congenital heart defect (30-50%)
- small VSD (majority)
- clinical presentation
  - history: asymptomatic, normal growth and development
  - physical exam: early systolic to holosystolic murmur, best heard at LLSB, thrill
investigations: ECG and CXR are normal; Echo to confirm diagnosis
management: most close spontaneously

- moderate-to-large VSD
  - epidemiology: CHF by 2 mo; late secondary pulmonary HTN if left untreated
  - clinical presentation
    - history: delayed growth, decreased exercise tolerance, recurrent URTIs or “asthma” episodes
    - physical exam: holosystolic murmur at LLSB, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur
  - investigations
    - ECG: LVH, LAH, RVH
    - CXR: increased pulmonary vasculature, cardiomegaly, CHF
    - Echo: diagnostic
  - management: treatment of CHF and surgical closure by 1 yr old

Patent Ductus Arteriosus
- patent vessel between descending aorta and left pulmonary artery (normally, functional closure within first 15 h of life, anatomical closure within first days of life)
- epidemiology
  - 5-10% of all congenital heart defects
  - delayed closure of ductus is common in premature infants (1/3 of infants <1,750 g); this is different from PDA in term infants
- natural history: spontaneous closure common in premature infants, less common in term infants
- clinical presentation
  - history: asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use, CHF
  - physical exam: tachycardia, bounding pulses, hyperactive precordium, wide pulse pressure, continuous “machinery” murmur best heard at left infraclavicular area
- investigations
  - ECG: may show left atrial enlargement, LVH, RVH
  - CXR: normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery
  - Echo: diagnostic
- management
  - indomethacin (Indocid®): antagonizes prostaglandin E2, which maintains ductus arteriosus patency; only effective in premature infants
  - catheter or surgical closure if PDA causes respiratory compromise, FTT, or persists beyond 3rd mo of life

2. OBSTRUCTIVE LESIONS
- present with decreased urine output, pallor, cool extremities and poor pulses, shock or sudden collapse

Coarctation of the Aorta
- definition: narrowing of aorta (almost always at the level of the ductus arteriosus)
- epidemiology: commonly associated with bicuspid aortic valve (50%); Turner syndrome (35%)
- clinical presentation
  - history: often asymptomatic
  - physical exam
    - blood pressure discrepancy between upper and lower extremities (increased suspicion/severity if >20 mmHg difference)
    - diminished or delayed femoral pulses relative to brachial (i.e. brachial-femoral delay)
    - possible systolic murmur with late peak at apex, left axilla, and left back
    - if severe, presents with shock in the neonatal period when the ductus arteriosis closes
- investigations: ECG shows RVH early in infancy, LVH later in childhood; Echo or MRI for diagnosis
- prognosis: can be complicated by HTN; if associated with other lesions (e.g. PDA, VSD) can lead to CHF
- management: give prostaglandins to keep ductus arteriosus patent for stabilization and perform surgical correction in neonates; for older infants and children balloon arterioplasty may be an alternative to surgical correction. The American Heart Association and the American College of Cardiology recommend that correction of coarctation should be done as early as possible to reduce long-term morbidity and increase survival

Aortic Stenosis
- 4 types: valvular (75%), subvalvular (20%), supravalvular, and idiopathic hypertrophic subaortic stenosis (5%)
- clinical presentation
  - history: often asymptomatic, but may be associated with CHF, exertional chest pain, syncope, or sudden death
  - physical exam: SEM at RUSB with aortic ejection click at the apex (only for valvular stenosis)
- diagnosis: Echo
- management: valvular stenosis is usually treated with balloon valvuloplasty, patients with subvalvular or supravalvular stenosis require surgical repair, exercise restriction required
Pulmonary Stenosis
- 3 types: valvular (90%), subvalvular, or supravalvular
- definition of critical pulmonary stenosis: inadequate pulmonary blood flow, dependent on ductus for oxygenation, progressive hypoxia and cyanosis
- natural history: may be part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with syndromes (e.g. congenital rubella, Noonan syndrome)
- clinical presentation
  - history: spectrum from asymptomatic to CHF
  - physical exam: wide split S2 on expiration, SEM at LSB, pulmonary ejection click (for valvular lesions)
- investigations
  - ECG: RVH
  - CXR: post-stenotic dilation of the main pulmonary artery
  - Echo: diagnostic
- management: surgical repair if critically ill or if symptomatic in older infants/children

Cyanotic Congenital Heart Disease
- systemic venous return re-enters systemic circulation directly
- most prominent feature is cyanosis (O₂ sat <75%)
- hyperoxic test differentiates between cardiac and other causes of cyanosis
  - obtain preductal, right radial ABG in room air, then repeat after the child inspires 100% O₂
  - if PaO₂ improves to greater than 150 mmHg, cyanosis less likely cardiac in origin
- pre-ductal and post-ductal pulse oximetry
  - >5% difference suggests R to L shunt

1. RIGHT-TO-LEFT SHUNT LESIONS

Tetralogy of Fallot
- epidemiology: 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy with peak incidence at 2-4 mo of age
- pathophysiology
  - embryological defect due to anterior and superior deviation of the outlet septum leading to: VSD, RVOTO (i.e. pulmonary stenosis), over-riding aorta, and RVH
  - infants may initially have a L → R shunt (therefore no cyanosis); however, RVOTO is progressive, leading to increasing R → L shunting with hypoxemia and cyanosis
  - degree of RVOTO determines the direction and degree of shunt and, therefore, the extent of clinical cyanosis and degree of RVH
- clinical presentation
  - history: hypoxic “tet” spells
    - during exertional states (crying, exercise) the increasing pulmonary vascular resistance and decrease in systemic resistance causes an increase in right-to-left shunting
  - clinical features include paroxysms of rapid and deep breathing, irritability and crying, increasing cyanosis, decreased intensity of murmur (decreased flow across RVOTO)
  - if severe, can lead to decreased level of consciousness, seizures, death
- physical exam
  - single loud S2 due to severe pulmonary stenosis (i.e. RVOTO), SEM at LSB
- investigations
  - ECG: RAD, RVH
  - CXR: boot-shaped heart, decreased pulmonary vasculature, right aortic arch (in 20%)
  - Echo: diagnostic
- management of spells: O₂, knee-chest position, fluid bolus, morphine sulfate, propranolol
- treatment: surgical repair at 4-6 mo of age; earlier if marked cyanosis or “tet” spells

2. OTHER CYANOTIC CONGENITAL HEART DISEASES

Transposition of the Great Arteries (TGA)
- epidemiology: 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonates
- pathophysiology: parallel pulmonary and systemic circulations
  - systemic: body → RA → RV → aorta → body
  - pulmonary: lungs → LA → LV → pulmonary artery → lungs
- survival is dependent on mixing through PDA, ASD, or VSD
- physical exam
  - neonates: ductus arteriosus closure causes rapidly progressive severe hypoxemia unresponsive to oxygen therapy, acidosis, and death
  - VSD present: cyanosis is not prominent; CHF within first weeks of life
  - VSD absent: no murmur
• investigations
  ▪ ECG: RAD, RVH, or may be normal
  ▪ CXR: egg-shaped heart with narrow mediastinum (“egg on a string”)
  ▪ Echo: diagnostic
• management
  ▪ symptomatic neonates: prostaglandin E1 infusion to keep ductus open until balloon atrial septostomy
  ▪ surgical repair: arterial switch performed in the first two weeks in those without a VSD while LV muscle is still strong

Total Anomalous Pulmonary Venous Return
• epidemiology: 1-2% of CHD
• pathophysiology
  ▪ all pulmonary veins drain into right-sided circulation (systemic veins, RA)
  ▪ no direct oxygenated pulmonary venous return to left atrium
  ▪ often associated with obstruction at connection sites
  ▪ ASD must be present for oxygenated blood to shunt into the LA and systemic circulation
• management: surgical repair in all cases and required urgently for severe cyanosis

Truncus Arteriosus
• pathophysiology
  ▪ single great vessel gives rise to the aorta, pulmonary, and coronary arteries
  ▪ truncal valve overlies a large VSD
  ▪ potential for coronary ischemia with fall in pulmonary vascular resistance
• management: surgical repair within first 6 wk of life

Hypoplastic Left Heart Syndrome
• epidemiology: 1-3% of CHD; most common cause of death from CHD in first month of life
• pathophysiology: LV hypoplasia may include atretic or stenotic mitral and/or aortic valve, small ascending aorta, and coarctation of the aorta with resultant systemic hypoperfusion
• systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
• management
  ▪ intubate and correct metabolic acidosis
  ▪ IV infusion of prostaglandin E1 to keep ductus open
  ▪ surgical palliation (overall survival 50% to late childhood) or heart transplant

Congestive Heart Failure
• see Cardiology and Cardiac Surgery, C33

Etiology
• CHD
• cardiomyopathy (primary or secondary)
• high output circulatory states (e.g. anemia, AVMs, cor pulmonale, hyperthyroidism)
• non-cardiac (e.g. sepsis, renal failure)
• pressure overload (e.g. aortic stenosis/co-arcrtation, pulmonary stenosis, HTN)
• volume overload (e.g. L to R shunt, valve insufficiency)

History
• infant: feeding difficulties, early fatigability, diaphoresis while sleeping or eating, respiratory distress, lethargy, FTT
• child: decreased exercise tolerance, fatigue, decreased appetite, respiratory distress, frequent URTIs or “asthma” episodes
• orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all uncommon in children

Physical Findings
• 4 key features: tachycardia, tachypnea, cardiomegaly, hepatomegaly
• FTT
• alterations in peripheral pulses, four limb blood pressures (in some CHDs)
• dysmorphic features associated with congenital syndromes

Investigations
• CXR: cardiomegaly, pulmonary venous congestion
• ECG: sinus tachycardia, signs of underlying cause (heart block, atrial enlargement, hypertrophy, ischemia/infarct)
• Echo: structural and functional assessment
• blood work: CBC, electrolytes, BUN, Cr, LFTs
Management
- general: sitting up, O₂, sodium and water restriction, increased caloric intake
- pharmacologic: diuretics, afterload reduction (e.g. ACE inhibitor), β-blockers; digoxin rarely used
- curative: correction of underlying cause

Dysrhythmias
- see Cardiology and Cardiac Surgery, C15
- can be transient or permanent, congenital (structurally normal or abnormal) or acquired (toxin, infection, infarction)

Sinus Arrhythmia
- phasic variations with respiration (present in almost all normal children)

Sinus Tachycardia
- rate of impulses arising from sinus node is elevated (>150 bpm in infants, >100 bpm in older children)
- characterized by: beat-to-beat heart rate variability with changes in activity, P waves present/normal, PR constant, QRS narrow
- etiology: HTN, fever, anxiety, sepsis, anemia/hypoxia, PE, drugs, etc.
- differentiate from SVT (see below) by slowing the sinus rate (vagal massage, β-blockers) to identify sinus P waves

Premature Atrial Contractions
- may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitalis toxicity

Premature Ventricular Contractions
- common in adolescents
- benign if single, uniform, disappear with exercise, and no associated structural lesions
- if not benign, may degenerate into more severe dysrhythmias

Supraventricular Tachycardia
- abnormally rapid heart rhythm originating above the ventricles – most frequent sustained dysrhythmia in children
- no beat-to-beat HR variability, >220 bpm (infants) or >180 bpm (children), P waves absent/abnormal, PR indeterminable, QRS usually narrow
- pre-excitation syndromes (subset of SVT): WPW syndrome, congenital defect (see Cardiology and Cardiac Surgery, C21)

Complete Heart Block
- congenital heart block can be caused by maternal anti-Ro or anti-La (e.g. mother with SLE)
- often diagnosed in utero (may lead to development of fetal hydrops)
- clinical symptoms related to level of block (the lower the block, the slower the heart rate and greater the symptoms of inadequate cardiac output)
- symptomatic patients need a pacemaker

Heart Murmurs
- 50-80% of children have audible heart murmurs at some point in their childhood
- most childhood murmurs are functional (e.g. “innocent”) without associated structural abnormalities and have normal ECG and radiologic findings
- in general, murmurs can become audible or accentuated in high output states (e.g. fever, anemia)

Table 11. Differentiating Heart Murmurs

<table>
<thead>
<tr>
<th>Innocent</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Timing</td>
<td>SEM</td>
</tr>
<tr>
<td>Grade</td>
<td>&lt;3/6, soft/blowing/vibratory</td>
</tr>
<tr>
<td>Splitting</td>
<td>Physiologic S2</td>
</tr>
<tr>
<td>Extra Sounds/Clicks</td>
<td>None</td>
</tr>
<tr>
<td>Change of Position</td>
<td>Murmur varies</td>
</tr>
</tbody>
</table>
Table 12. Five Innocent Heart Murmurs

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Age</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Pulmonic Stenosis</td>
<td>Neonates, low-pitched, radiates to axilla and back</td>
<td>Neonates, usually disappears by 3-6 mo</td>
<td>PDA, Pulmonary stenosis</td>
</tr>
<tr>
<td>Still’s Murmur</td>
<td>Vibratory, LLS or apex, SEM</td>
<td>3-6 yr</td>
<td>Subaortic stenosis, Small VSD</td>
</tr>
<tr>
<td>Venous Hum</td>
<td>Infraclavicular hum, continuous, R&gt;L</td>
<td>3-6 yr</td>
<td>PDA</td>
</tr>
<tr>
<td>Pulmonary Ejection</td>
<td>Soft, blowing, LUSB, SEM</td>
<td>8-14 yr</td>
<td>ASD, Pulmonary stenosis</td>
</tr>
<tr>
<td>Supraclavicular Arterial Bruit</td>
<td>Low intensity, above clavicles</td>
<td>Any age</td>
<td>Aortic stenosis, Bicuspid aortic valve</td>
</tr>
</tbody>
</table>

Infective Endocarditis

- see Infectious Diseases, ID17

Development

Approach to Global Developmental Delay

- also known as Early Developmental Impairment

Definition

- performance significantly below average in two or more domains of development
- when persistent, these become developmental disabilities, which are lifelong impairments

Epidemiology

- 5-10% of children have neurodevelopmental delay
- careful evaluation can reveal a cause in 50-70% of cases

Etiology

- CNS abnormalities (meningitis/encephalitis, brain malformation, trauma, etc.)
- sensory deficits (hearing, vision)
- environmental (psychosocial neglect, lead exposure, antenatal drug or alcohol exposure, etc.)
- genetic/chromosomal disorders (DS, Fragile X, etc.)
- metabolic disorders (inborn errors of metabolism, hypothyroidism, etc.)
- obstetrical (prematurity, HIE, TORCH infections, etc.)

Clinical Presentation

- history
  - intraterine exposures, perinatal events
  - detailed developmental milestones: rate of acquisition, regression of skills
  - associated problems: feeding, seizures, behavior, sleep
  - family history, consanguinity
  - social history
- physical exam
  - dysmorphic features, hepatosplenomegaly, neurocutaneous markers, growth parameters, detailed neurological examination
- investigations
  - neurodevelopmental assessment, vision and hearing test, psychosocial evaluation, OT, PT and/or SLP assessments, genetics consultation
  - laboratory testing and imaging (guided by history and physical exam)
    - microarray, chromosomes, FISH, Fragile X testing, neuroimaging, metabolic workup, neuroelectrophysiologic testing

Management

- dependent on specific area of delay
- therapy services (e.g. speech and language therapy for language delay, OT and/or PT for motor delay), early intervention services (e.g. infant development services)
**Intellectual Disability**

**Definition**
- state of functioning that begins in childhood and is characterized by limitations in both intelligence and adaptive skills
- historically defined as an IQ <70

**Epidemiology**
- 1% of general population; M:F = 1.5:1

**Etiology**
- any disorder that interferes with brain development and functioning
- prenatal (majority): TORCH infections, FASD
- genetic/metabolic: DS, Fragile X, PKU, untreated or delayed diagnosis of congenital hypothyroidism, CNS abnormalities, other chromosomal/metabolic disorders

**Risk Factors**
- male, consanguineous parents, family history, older maternal age, decreasing maternal education, certain ethnicities
- prenatal: pre-eclampsia, maternal malnutrition or DM
- perinatal: prematurity, low birth weight, birth trauma/hypoxia
- postnatal: ICH, CNS or other serious infection, hypoxia, environmental toxins, psychosocial deprivation, malnutrition

**Clinical Presentation**
- history
  - well below average general intellectual functioning
  - significant deficits in adaptive functioning in at least two of: communication, self-care, home-living, social skills, self-direction, academic skills, work, leisure, health, safety
- physical exam
  - check growth, dysmorphic features, complete physical exam
- investigations
  - standardized psychology assessment (includes IQ test and measure of adaptive functioning)
  - vision, hearing, and neurologic assessment
  - genetic and metabolic testing as indicated

**Management**
- main objective: enhance adaptive functioning level
- requires an interprofessional team with strong case co-ordination
- emphasize community-based treatment and early intervention
- individual/family therapy, behavior management services, therapy services (e.g. OT, SLP), medications for associated conditions
- education: life skills, vocational training, communication skills, family education
- psychosocial support for individual and family; respite care

**Prognosis**
- higher rates of sensory deficits, motor impairment, behavioral/emotional disorders, seizures, psychiatric illness

**Language Delay**

**Definition**
- no universally accepted definition, but often identified around 18 mo of age with enhanced well baby visit
- if formally tested, performance on a standardized assessment of language is at least one standard deviation below mean of age
- can be expressive (ability to produce or use language), receptive (ability to understand language), or both

**Epidemiology**
- ~10-15% of 2 yr children have a language delay, but only 4-5% remain delayed after 3 yr
- ~6-8% of school-aged children have specific language impairment (many of whom were not identified before school entry)
Etiology

- cognitive disability
- constitutional language delay
- genetic/metabolic: DS, Fragile X syndrome, Williams syndrome, hypothyroidism, PKU, etc.
- hearing impairment
- mechanical problems: cleft palate, cranial nerve palsy
- medical condition: seizure disorder (includes acquired epileptic aphasia), CP, TORCH infection, iron deficiency, lead poisoning, etc.
- autism spectrum disorder
- psychosocial: neglect or abuse
- selective mutism

Risk Factors

- male, positive family history, prematurity, psychosocial (poverty, low parental education, maternal depression)

Clinical Presentation

- history
  - concerns about hearing, delay in language development or regression in previously normal language development
  - delayed language milestones on well-child check up; presence of red flags
  - must determine if language delay is expressive, receptive, or mixed
  - children with expressive language delays may have concurrent behavior problems or drooling (because of abnormal oral musculature)
  - risk factors for hearing loss (hereditary, recurrent AOM) and language delay
- physical exam
  - guided by history: look for abnormal growth, dysmorphisms, unusual social interactions (lack of eye contact, not pointing)
  - include full exam of the external/internal ear (e.g. TM scarring), oral pharynx (e.g. cleft palate), and neurologic system (including tone)
- investigations
  - use of language specific screens in primary care setting: The Early Language Milestone, CAT/CLAMS, MCHAT, etc.
  - all children with suspected language delay MUST be referred to an audiologist for a hearing assessment
  - CBC (to rule out anemia), venous blood lead levels, genetic/metabolic workup as indicated

Management

- specific to etiology
- often multidisciplinary and requires appropriate referrals: early intervention services, special education services, SLP, OHNS and dental professionals, general support services
- primary care provider can help reinforce family’s understanding of delay and provide follow-up and care coordination
- prevention: parents can read aloud to their child, engage in dialogic reading, avoid baby talk, narrate daily activities, etc.

Prognosis

- depends on etiology
- if language delay persists beyond 5 yr old, more likely to have difficulties in adulthood
- persistent language delay is associated with poor academic performance, behavioral problems, social isolation

Fetal Alcohol Spectrum Disorder

Definition

- term describing the range of effects of prenatal exposure to alcohol, including physical, mental, behavioral, and learning disabilities
- no “safe” level of alcohol consumption during pregnancy has been established
- spectrum includes: FAS, partial FAS, ARBD, and ARND

Epidemiology

- prevalence of FAS and FASD is 0.1% and 1.0%, respectively
- most common preventable cause of intellectual disability

Pathogenesis

- specific mechanism of FASD is unknown, but hypotheses include nutritional deficits, toxic effects of acetaldehyde, alteration of placental transport, abnormal protein synthesis, and altered cerebral neurotransmission
Diagnosis
• often misdiagnosed or missed entirely
• diagnosis of FAS, ARBD, and ARND all require evidence of maternal drinking during pregnancy
• criteria for diagnosis of FAS
  ▪ growth deficiency: low birth weight and/or decelerating weight over time not due to nutrition
  ▪ characteristic pattern of facial anomalies: short palpebral fissures, flattened philtrum, thin upper lip, flat midface
  ▪ CNS dysfunction: microcephaly and/or neurobehavioral dysfunction (hyperactivity, fine motor problems, attention deficits, learning disabilities, cognitive disabilities, difficulties in adaptive functioning, etc.)
• criteria for diagnosis of ARBD
  ▪ congenital anomalies, including malformations and dysplasias of the cardiac, skeletal, renal, ocular, and auditory systems
• criteria for diagnosis of ARND
  ▪ CNS dysfunction (similar to FAS)
  ▪ complex pattern of behavioral or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone

Management
• early diagnosis is essential to prevent secondary disabilities
• no cure, but individuals with FASD and their families should be linked to community resources and services to improve outcome

Prognosis
• secondary disabilities include unemployment, mental health problems, difficulties with the law, inappropriate sexual behavior, disrupted school experience, peer problems

Learning Disabilities

Definition
• specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
• a significant discrepancy between a child’s intellectual ability and their academic performance
• several types: learning disabilities in reading, writing, mathematics

Epidemiology
• prevalence: 2-10%
• high incidence of psychiatric comorbidity: anxiety, dysthymia, conduct disorder, major depressive disorder, oppositional defiant disorder, ADHD

Etiology
• pathogenesis is unknown, likely genetic factors involved
• learning disabilities may be associated with a number of conditions:
  ▪ genetic/metabolic: Turner syndrome, Klinefelter syndrome
  ▪ perinatal: prematurity, low birth weight, birth trauma/hypoxia
  ▪ postnatal: CNS damage, hypoxia, environmental toxins, FAS, psychosocial deprivation (understimulation), malnutrition
• poor visual acuity is NOT a cause

Risk Factors
• positive family history, prematurity, other developmental and mental health conditions, neurologic disorders (e.g. seizure disorders, neurofibromatosis), history of CNS infection/irradiation/traumatic injury

Clinical Presentation
• history and physical exam
  ▪ school difficulties (academic achievement, behavior, attention, social interaction)
  ▪ development of negative self-concept → reluctance to participate even in areas of strength
  ▪ social issues: overt hostility towards parents/teachers; difficulties making friends for several reasons (problems remembering names, difficulties with language to engage in conversations, inability to understand games and complex rules, etc.), bullying, and anxiety
  ▪ look for dysmorphisms, complete physical exam
• investigations
  ▪ standardized tests for IQ
  ▪ individual scores on achievement tests in reading, mathematics, or written expression (WISC III, WRAT) >2 SD below that expected for age, education, and IQ
Management
• provide quality instruction for specific learning disability
• support student by modifying the curriculum and/or providing accommodations (e.g. scribe for writing, extra time for tests, photocopied notes, etc.)
• consider grade retention in certain students
• specialized education placements that can provide educational remediation

Prognosis
• limited information available about persistence of learning disabilities over time
• low self-esteem, poor social skills, 40% school drop-out rate

Motor Delay
• see Cerebral Palsy, P87 and Muscular Dystrophy, P45

Endocrinology

Antidiuretic Hormone

Diabetes Insipidus
• see Endocrinology, E19 and Nephrology, NP11

Syndrome of Inappropriate Antidiuretic Hormone
• see Endocrinology, E19 and Nephrology, NP9

Diabetes Mellitus

DIABETES MELLITUS TYPE 1
• insulin deficiency following destruction of the pancreatic β cells

Epidemiology
• most common form of DM in children, M=F
• variable prevalence internationally, affects ~1.7:1,000 children and adolescents in the US
• can present at any age, but bimodal peaks at 5-7 yr old and at puberty

Etiology
• type 1A: cell-mediated autoimmune destruction of β-cells of the pancreas
• type 1B: rare, non-immune variation; unknown cause
• disease results from some level of genetic predisposition and an environmental trigger
  ▪ human leukocyte antigen locus confers ~50% of genetic susceptibility
  ▪ trigger likely infectious and/or hormonal (as suggested by bimodal peaks in age of onset)

Risk Factors
• positive family history of type 1 DM, personal or family history of other autoimmune diseases

Clinical Presentation
• history
  ▪ initially presents as polyuria, often manifested as nocturia or secondary enuresis
  ▪ polydipsia, weight loss (lack of insulin leading to a catabolic state), and polyphagia
  ▪ DKA on initial presentation (~20%); vomiting, abdominal pain, confusion/lethargy
• physical exam
  ▪ tachypnea, signs of dehydration, ↓ LOC, Kussmaul's respiration, ketone breath
• investigations
  ▪ initial tests: urine dipstick (glucose, ketones), random blood glucose (200 mg/dL)
  ▪ DKA blood work: venous/arterial blood gas, osmolarity, plasma glucose, bicarbonate, HbA1c, serum ketones, BUN, Cr, electrolytes, CBC
  ▪ if etiology is unclear, consider ordering autoimmune antibodies (anti-Gad, anti-islet)

Management
• disclose diagnosis and prompt patient education around survival skills, meal plans, and insulin injections
• refer patient to diabetes team with pediatric expertise for education, ongoing care, and psychosocial support
• management is multidisciplinary and family-centered
• conventional insulin regimen
  ▪ 2/3 of total daily insulin dose in AM (1/3 rapid acting + 2/3 intermediate-acting)
  ▪ 1/3 of total daily insulin dose in PM (1/3 rapid acting + 2/3 intermediate-acting)

Diagnostic Criteria for DM (Types 1 and 2)
One of:
• HbA1c >6.5% (not validated in children)
• Fasting glucose ≥126 mg/dL
• 2 h plasma glucose during OGTT ≥200 mg/dL
• Random glucose ≥200 mg/dL with classic symptoms of hyperglycemia (polyuria, polydipsia, weight loss)

Blood Glucose Targets by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Pre-Meal Blood Glucose Target</th>
<th>HbA1c Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>100-180 mg/dL</td>
<td>&lt;8.5%</td>
</tr>
<tr>
<td>6-12</td>
<td>90-180 mg/dL</td>
<td>&lt;8%</td>
</tr>
<tr>
<td>13-19</td>
<td>90-150 mg/dL</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>&gt;19</td>
<td>As adult</td>
<td>&lt;7%</td>
</tr>
</tbody>
</table>
• intensive insulin regimen (multiple daily injections)
  ▪ studies show increased glycemic control with intensive vs. conventional dosing
  ▪ 1/2 of total daily insulin dose as long-acting insulin (either morning or bedtime)
  ▪ remainder of total daily insulin dose given as short or rapid-acting insulin divided before meals (dosage varies between meals depending on glucose content of meal and exercise/activity pattern)
  ▪ can also use insulin infusion pump
• blood glucose monitoring
  ▪ tight glycemic control decreases rate of long-term complications
  ▪ glycemic targets: age <6 fasting blood glucose (BG)100-180 mg/dL, HbA1c <8.5%; age 6-12 fasting BG 90-180 mg/dL, HbA1c ≤8%; age 13-19 fasting BG 90-150 mg/dL, HbA1c ≤7.5%
  ▪ for tighter control, may consider continuous subcutaneous insulin infusion (CSI) pump or MDI (multiple daily injections regimen; basal insulin plus analog for meals)
  ▪ young children are more susceptible to hypoglycemia
  ▪ if DKA present: ABCs, admit, monitors, correct fluid losses, administer insulin and restore glucose gradually, correct electrolyte disturbances, identify/treat precipitating event, avoid complications (i.e. cerebral edema)
  ▪ low threshold to investigate (CT/MRI) and treat DKA, as cerebral edema is a major concern
  ▪ see Endocrinology, E11
• screen for micro- and macrovascular complications (regular ophthalmology assessments, blood pressure, microalbuminuria), concurrent autoimmune diseases (thyroiditis, celiac disease, etc.), and mental health issues (depression, eating disorders)

**Prognosis**
• no cure currently
• short-term complications
  ▪ hypoglycemia
    ▪ due to missed/delayed meals, excess insulin or exercise, illness
    ▪ can lead to seizures and/or coma
    ▪ reversed with PO/IV glucose or IM glucagon
  ▪ hyperglycemia
    ▪ due to intercurrent illness, diet-to-insulin mismatch
    ▪ ↑ risk of end-organ damage
  ▪ DKA: due to missed insulin doses, infection; most common cause of death
• long-term complications
  ▪ microvascular: retinopathy, nephropathy, neuropathy
  ▪ macrovascular: metabolic syndrome, CVD, CAD, PVD
  ▪ increased risk of other autoimmune diseases

**DIABETES MELLITUS TYPE 2**
• see Family Medicine, FM22, Endocrinology, E6
• impaired glucose metabolism due to increased peripheral insulin resistance
• rare before 10 yr of age, but more common in older children/adolescents
• prevalence is rising mainly due to the increased incidence of childhood obesity
• risk factors: obesity, positive family history, female gender, certain ethnic groups
• clinical presentation may be similar to that of type 1 DM, though most children are asymptomatic
• may present in DKA or hyperglycemic hyperosmotic nonketotic state
• management
  ▪ criteria to start insulin: distinction between type 1 and type 2 DM unclear, child is ketotic or in ketoacidosis, random blood glucose ≥250 mg/dL, or HbA1c >9%
  ▪ initiate lifestyle modification program, including diet, weight loss, physical activity (moderate-to-vigorous activity for at least 60 min/d; screen time less than 2 h/d)
  ▪ start metformin as 1st line therapy at time of diagnosis
  ▪ glycemic target: HbA1c ≤7%
  ▪ if glycemic targets not achieved within 3-6 mo from diagnosis with lifestyle intervention alone, either metformin, glimepiride, or insulin should be initiated
  ▪ monitor HbA1c every 3 mo
  ▪ advise patient to monitor finger-stick blood glucose levels if on medication with risk of hypoglycemia, are changing medication regimen, have not met treatment goals, or have intercurrent illness
• prognosis: includes microvascular and macrovascular complications similar to type 1 DM

**Growth**

**APPROACH TO SHORT STATURE**

**Definition**
• short stature: height <3rd percentile
• poor growth evidenced by growth deceleration (height crosses major percentile lines, growth velocity <25th percentile)
**Epidemiology**
- ~2.5% of the population by definition

**Etiology**
- see sidebar

**Clinical Presentation**
- history and physical exam
  - plot on growth curve (special growth charts available for Turner syndrome, achondroplasia, DS)
  - assess for dysmorphic features, disproportionate short stature
  - risk factors for GH deficiency: previous head trauma, history of intracranial bleed or infection, head surgery or irradiation, positive family history, breech delivery
  - decreased growth velocity may be more worrisome than actual height
- investigations
  - calculate mid-parental height: children are usually in a percentile between their parents’ height
  - AP x-ray of left hand and wrist for bone age
  - remaining investigations guided by history and physical (e.g. TSH, sweat chloride, etc.)

**Management**
- depends on severity of problem as perceived by parents/child
- no treatment for non-pathological short stature, except for idiopathic short stature
- GH therapy: if administered at an early age, can help patients achieve adult height
- requirements
  - GH shown to be deficient by 2 different stimulation tests
  - growth velocity <3rd percentile or height <3rd percentile
  - bone age x-rays show unfused epiphyses/delayed bone age
- support and management of resultant self-image issues, social anxiety, etc.

---

**Short Stature**

- **IUGR**
  - Primordial
    - Height, weight, and head circumference are affected
    - Chromosomal (e.g. Turner, Down syndrome)
    - Teratogen, placental insufficiency, infection
  - Proportionate
  - Disproportionate
    - Skeletal dysplasia

- **No IUGR**
  - Normal Growth Velocity
  - Slow Growth Velocity

- **Constitutional Growth Delay**
  - Delayed puberty
  - May have family history of delayed puberty
  - May need short-term therapy with androgens/estrogens
  - Delayed bone age
  - Often mid-parental height is normal

- **Familial**
  - Normal bone age
  - Treatment not indicated
  - Family Hx of short stature

- **Endocrine** (height affected more than weight)
  - GH deficiency
  - Hypothyroidism/Hyperthyroidism
  - Hypercortisolism
  - Hypopituitarism
  - Adrenal insufficiency

- **Chronic disease** (weight affected more than height)
  - Cyanotic CHD
  - Celiac disease, IBD, CF
  - Chronic infections
  - Chronic renal failure (often height more affected)

- **Psychosocial neglect** (psychosocial dwarfism)
  - Usually decreased height and weight (decreased head circumference if severe)

---

**Figure 7. Approach to the child with short stature**

**TALL STATURE**
- height greater than two SD above the mean for a given age, sex, and race

**Etiology**
- constitutional/familial
- endocrine: Beckwith-Wiedemann syndrome, hyperthyroidism, hypophyseal gigantism, precocious puberty
- genetic: homocystinuria, Klinefelter syndrome, Marfan syndrome, Sotos syndrome
Hypercalcemia/Hypocalcemia/Rickets

• see Endocrinology, E39, E40, E45

Hyperthyroidism and Hypothyroidism

• may be congenital or acquired (for acquired causes, see Endocrinology, E20 and E26)

CONGENITAL HYPERTHYROIDISM

• also known as neonatal Graves' disease

Epidemiology

• ~1:25,000 neonates, M=F

Etiology

• results from transplacental passage of maternal thyroid stimulating antibodies from mother with a history of Graves' disease

Clinical Presentation

• history and physical exam
  ▪ clinical manifestations may be masked if mother on antithyroid treatment
  ▪ may present with tachycardia with CHF, heart murmur, goiter, craniosynostosis, irritability, poor feeding, FTT
• investigations
  ▪ serum levels of TSH and free T4 in all infants with suspected congenital hyperthyroidism, or infants born to mothers with Graves' disease

Management

• methimazole until antibodies cleared
• symptomatic treatment as needed (e.g. β-blockers to control tachycardia)

Prognosis

• if prompt and adequate treatment given, most neonates improve rapidly
• antibodies usually spontaneously cleared by 2-3 mo of life
• fetal or neonatal hyperthyroidism may have adverse effects on CNS development, leading to developmental and behavior problems

CONGENITAL HYPOTHYROIDISM

Epidemiology

• incidence: 1:4,000-1:20,000 newborns births; F:M = 2:1
• one of the most common preventable causes of intellectual disability

Etiology

• may be classified as permanent primary, central, or transient hypothyroidism
• ~85% of primary cases are sporadic (mostly thyroid dysgenesis), remaining 15% are hereditary (mostly inborn errors of thyroid synthesis)
• causes of transient hypothyroidism: maternal antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications

Clinical Presentation

• history and physical exam
  ▪ usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  ▪ prolonged jaundice, constipation, sluggish, hoarse cry, lethargy, poor feeding, macroglossia, coarse facial features, large fontanelles, umbilical hernia
• investigations
  ▪ diagnosis through newborn screening of TSH or free T4; abnormal results should be confirmed with serum levels from venipuncture

Management

• thyroxine replacement
Prognosis
• excellent outcome if treatment started within 1-2 mo of birth
• if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or
disability (mild to profound)

Sexual Development

AMBIGUOUS GENITALIA

Definition
• newborn or child whose gender is difficult to assign based on the appearance of genitalia
• subtype of DSD: a condition in which development of chromosomal, gonadal, or anatomic sex is
atypical
• subtypes: 46,XX DSD, 46,XY DSD, ovotesticular DSD (true hermaphrodite)

Epidemiology
• incidence of genital abnormalities at birth is as high as 1:300
• prevalence of complex anomalies with true sexual ambiguity much lower at ∼1:5,000

Etiology
• 46,XY DSD
  • inborn error of testosterone biosynthesis or Leydig cell hypoplasia
  • 5-α-reductase deficiency, androgen receptor deficiency, or insensitivity
  • LH/hCG unresponsiveness
• 46,XX DSD
  • virilizing CAH (most common)
  • maternal source: virilizing ovarian or adrenal tumors, untreated maternal CAH, placental
  aromatase deficiency
• ovotesticular DSD
  • both ovarian follicles and seminiferous tubules in the same patient with a 46,XX karyotype
  • mixed gonadal dysgenesis

Risk Factors
• parental consanguinity, positive family history of ambiguous genitalia, early childhood illness/
death, or primary amenorrhea, maternal medications during pregnancy (e.g. androgens,
progesterones, danazol, phenytoin, aminoglutethimide, endocrine disruptors)

Clinical Presentation
• history
  • thorough obstetrical history, including prenatal screens and maternal medications
  • family history: autosomal recessive pattern may suggest CAH, X-linked recessive pattern
    may suggest androgen insensitivity syndrome
• physical exam
  • male pseudohermaphrodite (XY): small phallus, hypospadias, undescended testicles
  • female pseudohermaphrodite (XX): clitoral hypertrophy, labioscrotal fusion
  • look for concurrent midline defects, dysmorphic features, and congenital abnormalities
• investigations
  • karyotype and genetic workup as indicated
  • blood work: electrolytes and renin (evidence of salt-wasting in CAH); 17-OH-progesterone,
    androgens, FSH, and LH
  • imaging: abdominal U/S to look for uterus, testicles, ovaries

Management
• depends on underlying etiology
• avoid announcement of probable sex or use of personal pronouns until all tests are complete
• continuous psychosocial support for parents and child during development
• elective surgical reconstruction of genitalia is sometimes possible

CONGENITAL ADRENAL HYPERPLASIA

Definition
• autosomal recessive disorder characterized by the partial or total defect of various synthetic
enzymes of the adrenal cortex required for cortisol and aldosterone production
Epidemiology
- occurs in ~1:15,000 live births
- most common cause of ambiguous genitalia

Etiology
- for biosynthetic pathways of adrenal cortex, see Endocrinology E29
- 21-OH responsible for ~95% of CAH cases
- results in \( \downarrow \) cortisol and aldosterone production with shunting toward \( \uparrow \uparrow \) androgens
- cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
- rarer causes include deficiencies in 11-OH, cholesterol desmolase, 17-OH, and 3-HSD

Clinical Presentation
- depends on which enzyme in cortisol synthesis pathway is defective
- presentation of 21-OH deficiency can be divided into
  - classic deficiency with salt wasting: inadequate aldosterone resulting in FTT, hyperkalemia, hyponatremia, hypoglycemia, acidosis
  - classic deficiency without salt wasting: simple virilizing type
  - non-classic: signs/symptoms of androgen excess (e.g. amenorrhea, precocious puberty, etc.)
- 21-OH deficiency screening is part of many newborn screening programs across North America
- high serum levels of 17-OH progesterone in random blood sample diagnostic for 21-OH deficiency

Management
- correct any abnormalities in fluids, electrolytes, or serum glucose
- provide glucocorticoids/mineralocorticoids as necessary, extra glucocorticoids in times of stress
- psychosocial support

Prognosis
- complications if untreated include virilization, acne, salt wasting, hypotension

NORMAL PUBERTAL DEVELOPMENT

Physiology
- puberty occurs with the maturation of the HPG axis
- \( \uparrow \) pulsatile release of GnRH \( \rightarrow \) \( \uparrow \) release of LH and FSH \( \rightarrow \) maturation of gonads, release of sex steroids \( \rightarrow \) secondary sexual characteristics
- adrenal production of androgens also required

Females
- onset: age 8-13 yr old (may start as early as 7 yr in girls of African descent)
- usual sequence
  1. thelarche: breast budding
  2. pubarche: axillary hair, body odor, mild acne
  3. growth spurt
  4. menarche: mean age 12.5 yr; indicates that growth spurt is almost complete; menses may be irregular in duration and length of cycle
- early puberty is common and often constitutional, late puberty is rare (rule out organic causes)

Males
- onset: age 9-14 yr old
- usual sequence
  1. testicular enlargement
  2. penile enlargement
  3. pubarche: axillary and facial hair, body odor, mild acne
  4. growth spurt: occurs later in boys
- early puberty is uncommon (rule out organic causes), late puberty is common and often constitutional
- gynecomastia (transient development of breast tissue) is a common self-limited condition seen in 50% of males during puberty (but any discharge from nipple or fixed mass should be investigated)

Tanner Staging
- scale used in pediatrics that defines physical measurements of development based on external primary and secondary sex characteristics
PRECOCIOUS PUBERTY

Definition
- development of secondary sexual characteristics 2-2.5 SD before population mean
- <8 yr old for females, <9 yr old for males

Epidemiology
- F>M = 1/10,000

Etiology
- usually idiopathic in females (90%), more suggestive of pathology in males (50%)
- central (GnRH dependent)
  - hypergonadotropic hypergonadism; hormone levels as in normal puberty
  - premature activation of the HPG axis
  - differential diagnosis: idiopathic or constitutional (most common in females), CNS
disturbances (tumors, hamartomas, post-meningitis, increased ICP, radiotherapy), NF,
primary severe hypothyroidism
- peripheral (GnRH independent)
  - hypogonadotropic hypergonadism
  - differential diagnosis: adrenal disorders (CAH, adrenal neoplasm), testicular/ovarian
tumor, gonadotropin/hCG secreting tumor (hepatoblastoma, intracranial teratoma, germinoma),
exogenous steroid administration, McCune-Albright syndrome, aromatase excess syndrome,
rarely hypothyroidism (Van Wyk-Grumbach syndrome)

Clinical Presentation
- history
  - symptoms of puberty, family history of precocious puberty, medical illness
- physical exam
  - growth velocity
    - prepubertal: 4-6 cm/yr
    - growth spurt: boys 8-10 cm/yr, girls 6-8 cm/yr
  - complete physical exam, including Tanner staging and neurological assessment
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH,
    TSH, free T4, DHEA-S, 17-OH-progesterone)
  - secondary tests: MRI head, pelvic U/S, ß-hCG, GnRH, and/or ACTH stimulation test

Figure 8. Tanner staging
Management
• indications for medical intervention to delay progression of puberty: rapid advancement of puberty, early age, risk of compromise of final adult height, psychological
• central causes: goals are to preserve height and alleviate psychosocial stress; GnRH agonists (e.g. leuprolide) most effective
• peripheral causes: goal is to limit effects of elevated sex steroids; treat underlying cause; medications that decrease the production of a specific sex steroid or block its effects (e.g. ketoconazole, spironolactone, tamoxifen, anastrozole), surgical intervention

DELAYED PUBERTY

Definition
• failure to develop secondary sex characteristics by 2-2.5 SD beyond the population mean
  ▪ for males: lack of testicular enlargement by 14 yr old
  ▪ for females: lack of breast development by 13 yr old OR absence of menarche by 16 yr old or within 5 yr of pubertal onset

Epidemiology
• M>F

Etiology
• usually constitutional delay in males, more suggestive of pathology in females
• central causes
  ▪ constitutional delay in activation of HPG axis (most common)
  ▪ hypogonadotropic hypogonadism
• peripheral causes
  ▪ hypergonadotropic hypogonadism (e.g. primary gonadal failure, gonadal damage, Turner syndrome, hormone deficiency, androgen insensitivity syndrome, etc.)

Clinical Presentation
• history: weight loss, short stature, family history of puberty onset, medical illness, high performance athletes (females)
• physical exam: growth velocity (minimum 4 cm/yr), Tanner staging, neurological exam, complete physical exam
• investigations
  ▪ initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, IGF-1), CBC, electrolytes, BUN, Cr, LFTs, liver enzymes, ESR, CRP, urinalysis
  ▪ secondary tests: MRI head, pelvic U/S, karyotype, IBD panel, celiac disease panel, LH levels following GnRH agonist

Management
• identify and treat underlying cause
• hormonal replacement: cyclic estradiol and progesterone for females, testosterone for males

Gastroenterology

Vomiting

History
• characteristic of emesis (e.g. projectile, bilious, bloody)
• pattern of emesis (e.g. association with feeds, cyclic, morning)
• red flags: bilious or bloody emesis, projectile vomit, abdominal distension and tenderness, high fever, signs of dehydration
• note that vomiting without diarrhea is most likely not gastroenteritis

Physical Findings
• vital signs to determine clinical status and hydration state

Investigations
• CBC, electrolytes, BUN, Cr, amylase, lipase, glucose done routinely
• in sick child, add: ESR, venous blood gases, C&S (blood, stool), imaging
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Common Differential Diagnosis</th>
<th>Suggestive Findings</th>
<th>Diagnostic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEONATES – NON-BILIOUS</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>TEF</td>
<td>Vomiting, excessive secretions soon after birth (e.g. drooling, choking, respiratory distress), inability to feed, inability to advance NG tube</td>
<td>Inability to advance NG tube, CXR, upper GI series with water-soluble contrast</td>
</tr>
<tr>
<td></td>
<td>Pyloric stenosis</td>
<td>Projectile vomiting immediately after feeding, dehydrated, palpable “olive” in RUD, decreased stools, hunger</td>
<td>U/S of pylorus, upper GI study (if U/S not diagnostic), Electrolytes, ABG (hypokalemic, hypochloremic metabolic alkalosis)</td>
</tr>
<tr>
<td></td>
<td>GERD</td>
<td>Fussiness after feeds, spit ups, arching of back, poor weight gain</td>
<td>Empiric trial of acid suppression, pH monitoring study, upper GI study, endoscopy</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>Fever, lethargy, tachycardia, tachypnea, widening pulse pressure</td>
<td>CBC, cultures (blood, urine, CSF), CXR</td>
</tr>
<tr>
<td></td>
<td>Inborn error of metabolism</td>
<td>Poor feeding, FTT, jaundice, hepatosplenomegaly, cardiomyopathy, dysmorphia, developmental delay</td>
<td>Electrolytes, ABG (hyponatremic, hyperkalemic metabolic acidosis), lactate, ammonia, LFTs, BUN, Cr, serum glucose, bilirubin, PT/PTT, CBC</td>
</tr>
<tr>
<td>NEONATES – BILIOUS</td>
<td>Malrotation with volvulus</td>
<td>Bilious emesis, abdominal distension, pain, bloody stool, shock</td>
<td>AXR, upper GI series, contrast enema</td>
</tr>
<tr>
<td></td>
<td>Duodenal atresia</td>
<td>Bilious emesis, abdominal distension, often seen in DS, jaundice, polyhydramnios during pregnancy</td>
<td>AXR, upper GI series (‘double bubble’ sign)</td>
</tr>
<tr>
<td></td>
<td>Hirschsprung’s disease</td>
<td>Bilious emesis, abdominal distension, pain, failure to pass stool</td>
<td>AXR, upper GI series, contrast enema, rectal biopsy</td>
</tr>
<tr>
<td>CHILDREN AND ADOLESCENTS</td>
<td>Gastroenteritis</td>
<td>Diarrhea, fever, sick contact, recent travel</td>
<td>CBC, stool culture</td>
</tr>
<tr>
<td></td>
<td>Appendicitis</td>
<td>Periumbilical discomfort that later localizes to RLO, fever, anorexia</td>
<td>Abdominal U/S</td>
</tr>
<tr>
<td></td>
<td>Intussusception</td>
<td>Colicky progressive abdominal pain, drawing of leg up to chest, lethargy, bloody stool</td>
<td>Abdominal U/S</td>
</tr>
<tr>
<td></td>
<td>Non-GI infection (e.g. meningitis)</td>
<td>Fever, localized findings depending on cause</td>
<td>Cultures (CSF, blood, urine), brain imaging, CXR</td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
<td>Nocturnal waking, progressive recurrent headache worse with Valsalva, nuchal rigidity</td>
<td>Brain CT without contrast, Therapeutic LP in idiopathic intracranial HTN</td>
</tr>
<tr>
<td></td>
<td>Toxic ingestion</td>
<td>Finding possibly varying by substance-toxidrome, often a history of ingestion</td>
<td>Qualitative and sometimes quantitative levels (urine j-hCG, blood)</td>
</tr>
<tr>
<td></td>
<td>Pregnancy</td>
<td>Amenorrhea, morning sickness, bloating, breast tenderness</td>
<td>Urine j-hCG</td>
</tr>
<tr>
<td></td>
<td>Cyclic vomiting</td>
<td>At least 3 self-limited episodes of vomiting lasting 12 h, 7 d between episodes, no organic cause of vomiting</td>
<td>Diagnosis of exclusion</td>
</tr>
</tbody>
</table>

**Management**
- rehydration (see Fluids and Electrolytes, P78)
- treat underlying cause

**Gastroesophageal Reflux**

**Epidemiology**
- extremely common in infancy (up to 50%)

**Clinical Presentation**
- vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<30 mL)

**Investigations**
- thriving baby requires no investigation
- investigations required if concomitant FTT, feeding aversion, recurrent cough, pneumonia or bronchospasm, GI blood loss or symptoms persist after 18 mo
Management
• conservative: thickened feeds, frequent and smaller feeds
• medical
  ▪ short-term parenteral feeding to enhance weight gain
  ▪ ranitidine, PPI: decreases gastric acidity, decreases esophageal irritation
  ▪ domperidone, metoclopramide: improves gastric emptying and GI motility; safety concerns
    and limited efficacy, should be reserved for children with gastroparesis contributing to
    GERD
• surgical: indicated for failure of medical therapy (Nissen fundoplication)

Complications
• esophagitis, strictures, Barrett’s esophagus, FTT, aspiration, oral feeding aversion

Tracheoesophageal Fistula
• see General Surgery, GS64

Pyloric Stenosis
• see General Surgery, GS61

Duodenal Atresia
• see General Surgery, GS63

Malrotation of the Intestine
• see General Surgery, GS62

Diarrhea
• definition of diarrhea varies with diet and age (stool normalcy difficult to define in children)
• infants → increase in stool frequency to twice as often per day; older children → 3+ loose or
  watery stools/d
• duration: acute: <2 wk; chronic: >2 wk

Pathophysiology
• osmotic: due to non-absorbable solutes in GI tract (e.g. lactose intolerance)
• secretory: increased secretion of Cl– ions and water in intestinal lumen (e.g. bacterial toxin)
• malabsorption: decreased GI surface area (e.g. short bowel syndrome)

History
• frequency, duration, quality of diarrhea
• associated symptoms (e.g. fever, abdominal pain, hematochezia, etc.)
• recent antibiotic use or recent travel
• elements of diet

Physical Findings
• vital signs to determine clinical status and hydration state

Investigations
• acute diarrhea
  ▪ stool for C&S, O&P, electron microscopy for viruses, C. difficile toxin, microscopy
    (leukocytes suggestive of invading pathogen), blood and urine cultures, blood work
• chronic diarrhea
  ▪ serial heights, weights, growth percentiles
  ▪ if child growing well and thriving, workup is limited (stool cultures as above, stool reducing
    substances)
  ▪ red flags: poor growth, chronic rash, other serious infections, hospitalizations for
    dehydration
    ▪ require full workup (as per below)
  ▪ stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, C. difficile
    toxin, 3 d fecal fat, α-1-antitrypsin clearance, fecal elastase
  ▪ urinalysis, urine culture
  ▪ CBC, differential, ESR/CRP, smear, electrolytes, total protein, albumin, carotene, Ca2+, PO43–,
    Mg2+, Fe, ferritin, folate, fat-soluble vitamins, PTT, INR

Diarrhea is defined as an increase in frequency and/or decreased consistency
of stools compared to normal

Normal stool volume:
Infants: 5-10 g/kg/d
Children: 200 g/d

Diarrhea Red Flags
Bloody stool, fever, petechiae or purpura, signs of severe dehydration, weight loss/FTT

Indications for Medical Evaluation of Acute Diarrhea
• Age <6 mo
• Fever
• Visible blood in stool
• Frequent, substantial volume of diarrhea
• Signs of dehydration
• Change in mental status

MMWR Recomm Rep 2003:52(RR-16):1-16
- sweat chloride, celiac screen, thyroid function tests, urine VMA and HVA, HIV test, lead levels
- CXR, upper GI series and follow-through
- specialized tests: endoscopy, small bowel biopsy

### Differential Diagnosis

#### Table 14. Differential Diagnosis of Diarrhea

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Non-infectious</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>Rotavirus</td>
</tr>
<tr>
<td>Norwalk</td>
<td>Campylobacter</td>
</tr>
<tr>
<td>Enteric adenovirus</td>
<td>Shigella</td>
</tr>
<tr>
<td>Pathogenic E. coli</td>
<td>C. difficile</td>
</tr>
<tr>
<td>Enteropathogenic E. coli</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chronic</strong></td>
<td></td>
</tr>
<tr>
<td>0 – 3 mo</td>
<td>3 mo – 3 yr</td>
</tr>
<tr>
<td>GI infection</td>
<td>GI infection</td>
</tr>
<tr>
<td>Toddler’s diarrhea</td>
<td>Lactase deficiency</td>
</tr>
<tr>
<td>Toddler’s diarrhea</td>
<td></td>
</tr>
<tr>
<td>GI infection</td>
<td>IBD</td>
</tr>
<tr>
<td>Disaccharidase deficiency</td>
<td>Endocrine (thyrotoxicosis, Addison’s)</td>
</tr>
<tr>
<td>Cow’s milk protein intolerance</td>
<td>Neoplastic (pheochromocytoma, lymphoma)</td>
</tr>
<tr>
<td>CF</td>
<td></td>
</tr>
</tbody>
</table>

### Gastroenteritis

#### History
- non-specific: diarrhea, vomiting, fever, anorexia, headache, myalgias, abdominal cramps
- bacterial and parasitic agents more common in older children (2–4 yr)
- recent infectious contacts: symptoms usually begin 24–48 h after exposure

#### Physical Exam
- febrile
- dehydrated: must assess extent (see Dehydration, P78)

#### Investigations
- not usually necessary in young children
- stool analysis: leukocytes/erythrocytes suggests bacterial or parasitic etiology; pH <6 and presence of reducing substances suggests viral etiology

#### Complications
- viral gastroenteritis usually self-limiting (lasts 3–7 d in most cases)
- adverse effects related to hypovolemia, shock, tissue acidosis, and rapid onset and over-correction of electrolyte imbalances
- death in severe dehydration (rare in developed countries)

#### Table 15. Gastroenteritis

<table>
<thead>
<tr>
<th>Viral Infection</th>
<th>Bacterial Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Most common cause of gastroenteritis</td>
</tr>
<tr>
<td>Commonly: rotaviruses (most common), enteric adenovirus, norovirus (typically older children)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Associated with URTIs</td>
</tr>
<tr>
<td>Resolves in 3-7 d</td>
<td></td>
</tr>
<tr>
<td>Slight fever, malaise, vomiting, vague abdominal pain</td>
<td>Bloody diarrhea</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Day care, young age, sick contacts, immunocompromised</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Prevention and treatment of dehydration most important (see Dehydration, P78)</td>
</tr>
<tr>
<td>Early refeeding advisable, start with small amounts of easily digested carbohydrates, postpone dairy and fibrous vegetables</td>
<td>May return to age-appropriate diet once rehydrated and vomiting stops</td>
</tr>
<tr>
<td>May return to age-appropriate diet once rehydrated and vomiting stops</td>
<td>Avoid emetics improve vomiting, but worsen diarrhea</td>
</tr>
<tr>
<td>Antibiotic or antiparasitic therapy when indicated, antidiarrheal medications not indicated</td>
<td>Notify Public Health authorities if appropriate</td>
</tr>
<tr>
<td>Notify Public Health authorities if appropriate</td>
<td>Promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission</td>
</tr>
<tr>
<td>Promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission</td>
<td>Rotavirus vaccine</td>
</tr>
</tbody>
</table>
Toddler’s Diarrhea

**Epidemiology**
- most common cause of chronic diarrhea during infancy
- onset between 6-36 mo of age, ceases spontaneously between 2-4 yr

**Clinical Presentation**
- diagnosis of exclusion in thriving child
- 4-6 bowel movements per day
- diet history (e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption)
- stool may contain undigested food particles
- excoriated diaper rash

**Management**
- reassurance that it is self-limiting
- 4Fs (adequate Fiber, normal Fluid intake, 35-40% Fat, discourage excess Fruit juice)

Lactase Deficiency (Lactose Intolerance)

**Clinical Presentation**
- chronic, watery diarrhea and abdominal pain, bloating associated with dairy intake
- primary lactose intolerance: crampy abdominal pain with loose stool (older children, usually of East Asian and African descent)
- secondary lactose intolerance: older infant, persistent diarrhea (post viral/bacterial infection, celiac disease, or IBD)

**Diagnosis**
- trial of lactose-free diet
- watery stool, acid pH, positive reducing sugars
- positive breath hydrogen test if >6 yr

**Management**
- lactose-free diet, soy formula
- lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

Irritable Bowel Syndrome

- see Gastroenterology, G23

Celiac Disease

- see Gastroenterology, G18
- in children: presents at any age, usually 6-24 mo with the introduction of gluten in the diet
- FTT with poor appetite, irritability, apathy, rickets, wasted muscles, flat buttocks, rarely distended abdomen
- GI symptoms: anorexia, N/V, edema, anemia, abdominal pain
- non-GI manifestations: iron-deficiency anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty, behavioral changes
- associated with other autoimmune disorders

Milk Protein Allergy

**Pathophysiology**
- immune-mediated mucosal injury (IgE- and non-IgE-mediated)

**Clinical Presentation**
- up to 30% of children intolerant to cow’s milk may be intolerant to soy protein as well
- often history of atopy
- can present as
  - proctocolitis: mild diarrhea, small amounts of bloody stools (common presentation in young infant)
  - enterocolitis: vomiting, diarrhea, anemia, hematochezia
  - enteropathy: chronic diarrhea, hypoalbuminemia

Celiac disease is associated with an increased prevalence of IgA deficiency.
Since tTG is an IgA-detecting test, you must order an accompanying IgA level

A Celiac disease diet must avoid gluten present in “BROW” foods
Barley
Rye
Oats (controversial)
Wheat
Management

- casein hydrolysate formula (dairy-free e.g. Nutramigen®, Pregestimil®) or mother may remove all milk protein from diet and continue breastfeeding (with adequate calcium and vit D intake)
- often outgrow by 1 yr of age

Inflammatory Bowel Disease

- see Gastroenterology, G19

Cystic Fibrosis

- see Respirology, P92

Constipation

- decreased stool frequency (<3 stools/wk) and/or stool fluidity (hard, pellet-like)

FUNCTIONAL CONSTIPATION

- 99% of cases of constipation
- Rome III criteria; ≥2 of the following
  - ≤2 defecations in the toilet/wk
  - ≥1 episode of fecal incontinence/wk
  - history of retentive posturing or excessive volitional stool retention
  - history of painful or hard bowel movements
  - large fecal mass in rectum
  - history of large diameter stools that may obstruct toilet

Pathophysiology

- lack of fiber in diet or change in diet, poor fluid intake, behavioral
  - infants: often occurs when introducing cow's milk after breast milk due to high fat and solute content, lower water content
  - toddlers/older children: can occur during toilet training, or due to pain on defecation, leading to withholding of stool
  - two crucial time periods: toilet training and starting school

Management

- education: explanation of mechanism of functional constipation for parents/older children
- clean out: oral (PEG, mineral oil, or other oral laxatives) or rectal (phosphate soda, saline, or mineral oil enemas), or combination
- maintenance: adequate fluid intake (if <6 mo, 150 mL/kg/d), adequate dietary fiber (fruit, vegetables, whole grains), stool softening (PEG 3350, mineral oil), appropriate toilet training technique (dedicated time for defecation: 3-10 min, 1-2 x/d)
- children should be treated for at least 6 mo, and should not be weaned from maintenance therapy until they are having regular bowel movements without difficulty
- regular follow-up with ongoing support and encouragement is essential

Complications

- pain retention cycle: anal fissures + pain → withhold passing stool → chronic dilatation ± overflow incontinence

HIRSCHSPRUNG’S DISEASE (Congenital Aganglionic Megacolon)

- see General Surgery, GS63

OTHER ORGANIC DISORDERS CAUSING CONSTIPATION

- endocrine: hypothyroidism, DM, hypercalcemia
- neurologic: spinal cord abnormalities/trauma, NF
- anatomic: bowel obstruction, anus (imperforate, atresia, stenosis, anteriorly displaced)
- drugs: lead, chemotherapy, opioids
- others
Abdominal Pain

ACUTE ABDOMINAL PAIN

History
• description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
• associated symptoms: N/V, diarrhea, fever

Physical Exam
• abdominal exam, peritoneal signs, bowel sounds, rectal exam, rash

Investigations
• CBC, differential, urinalysis to rule out UTI

Table 16. Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Hepatobiliary Tract</th>
<th>Genitourinary</th>
<th>Hematologic</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td>Cholecystitis</td>
<td>Nephrolithiasis</td>
<td>Henoch-Schönlein purpura</td>
<td>DKA</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Pancreatitis</td>
<td>Testicular torsion</td>
<td>Sickel cell crisis</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Meckel’s diverticulum</td>
<td>UTI</td>
<td>Ovarian torsion</td>
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<tr>
<td>Mesenteric adenitis</td>
<td>Nephrolithiasis</td>
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<tr>
<td>Ileus</td>
<td>Testicular torsion</td>
<td>Endometriosis</td>
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<tr>
<td>Intestinal obstruction</td>
<td>Cholecystitis</td>
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<tr>
<td>(incarcerated hernia, intussusception, volvulus)</td>
<td>Pancreatitis</td>
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<tr>
<td>Malabsorption</td>
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<tr>
<td>IBS</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Cholecystitis</td>
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<tr>
<td>Pancreatitis</td>
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<tr>
<td>Ovarian torsion</td>
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<tr>
<td>Ectopic pregnancy</td>
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<tr>
<td>PID</td>
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<tr>
<td>Endometriosis</td>
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<td>Menstruation</td>
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<td>Henoch-Schönlein purpura</td>
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<tr>
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<td>Pneumonia</td>
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<tr>
<td>Somatization</td>
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</tbody>
</table>

APPENDICITIS
• see General Surgery, GS28
• most common cause of acute abdomen after 5 yr of age
• clinical features: low grade fever, abdominal pain, anorexia, N/V (after onset of pain), peritoneal signs (generalized peritonitis is a common presentation in infants/young children)
• treatment: surgical
• complications: perforation (common in young children), abscess

INTUSSUSCEPTION
• telescoping of segment of bowel into distal segment causing ischemia and necrosis

Epidemiology
• 90% idiopathic, children with CF or GJ tube at significantly increased risk; M:F = 3:1
• 50% between 3-12 mo, 75% before 2 yr of age

Pathophysiology
• usual site: ileocecal junction; jejunum in children with GJ tubes
• lead point of telescoping segment may be swollen Peyer’s patches, Meckel’s diverticulum, polyp, malignancy, HSP, structural abnormalities

Clinical Presentation
• “classic triad” (<25%) patients – abdominal pain, palpable mass, red currant jelly stools
• often preceded by URTI
• sudden onset of recurrent, paroxysmal, severe periumbilical pain with pain-free intervals
• later vomiting (may be bilious) and rectal bleeding (late finding)
• shock and dehydration; lethargy may be only presenting symptom

Diagnosis
• U/S, air enema

Management
• air enema can be therapeutic (reduces intussusception in 75% of cases), reduction under hydrostatic pressure, surgery rarely needed
• recurrence rate 10-15%, need to consider pathologic lead point
**Chronic Abdominal Pain**

**Epidemiology**
- prevalence: 10% of school children (peak at 8-10 yr), F>M

**Etiology**
- organic (<10%)
  - gastrointestinal
    - constipation (cause vs. effect), infectious
    - IBD, esophagitis, peptic ulcer disease, lactose intolerance
    - anatomic anomalies, masses
    - pancreatic, hepatobiliary
  - genitourinary causes: recurrent UTI, nephrolithiasis, chronic PID, Mittelschmerz
  - neoplastic
- functional abdominal pain (90%): can be diagnosed when there are no alarm symptoms or signs, physical exam is normal, and stool sample tests are negative for occult blood; no further testing is required, unless high suspicion for organic cause

**Clinical Presentation**
- clustering episodes of vague, crampy periumbilical/epigastric pain, vivid pain description
- seldom awakens child from sleep, less common on weekends
- aggravated by exercise, alleviated by rest
- psychological factors related to onset and/or maintenance of pain, school avoidance
- psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
- diagnosis of exclusion

**Investigations**
- fecal occult blood and others based on clinical suspicion (CBC, ESR, urinalysis, etc.)

**Management**
- continue to attend school
- manage any emotional or family problems, counseling, CBT
- trial of high fiber diet, trial of lactose-free diet
- possible role for amitriptyline
- reassurance

**Prognosis**
- pain resolves in 30-50% of children within 2-6 wk of diagnosis
- 30-50% of children with functional abdominal pain have functional pain as adults (e.g. IBS)

### Abdominal Mass

**Table 17. Differential Diagnosis for Abdominal Mass**

<table>
<thead>
<tr>
<th></th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal (note: 50% of abdominal masses in newborn are renal in origin)</td>
<td>Hydronephrosis</td>
<td>Nephroblastoma (Wilms’ tumor)</td>
</tr>
<tr>
<td></td>
<td>Polycystic kidney disease</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>Hamartoma</td>
<td></td>
</tr>
<tr>
<td>Adrenal</td>
<td>Ovarian cysts</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>Ovarian</td>
<td>Hepatomegaly/splenomegaly</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>Other</td>
<td>Pyloric stenosis</td>
<td>Rhabdomyosarcoma</td>
</tr>
<tr>
<td></td>
<td>Abdominal hernia</td>
<td>Retropertoneal sarcoma</td>
</tr>
<tr>
<td></td>
<td>Tenotomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fecal impaction</td>
<td></td>
</tr>
</tbody>
</table>

**Upper Gastrointestinal Bleeding**
- see Gastroenterology: G25


**Lower Gastrointestinal Bleeding**

- see Gastroenterology, G27

**Etiology**

- **acute**
  - infectious (bacterial, parasitic)
  - antibiotic-induced (C. difficile)
  - NEC in preterm infants
  - anatomic
  - malrotation/volvulus, intussusception
  - Meckel’s diverticulitis
  - anal fissures, hemorrhoids
  - vascular/hematologic
  - HSP
  - HUS
  - coagulopathy

- **chronic**
  - anal fissures (most common)
  - colitis
  - IBD
  - allergic (milk protein)
  - structural
  - polyps (most are hamartomas)
  - neoplasms (rare)
  - coagulopathy

**Physical Exam**

- hemodynamic status, evidence of FTT, fever
- anal and rectal exam: tags, fissures, anal fistulas, polyps, foreign body, blood per rectum
- stool appearance
- NG aspirate
- lower GI bleed may present as melena (if it involves the small bowel) or hematochezia

**Investigations**

- stool cultures (C&S, C. difficile toxin)
- urinalysis and microscopy
- CBC, smear, differential, ESR, CRP, electrolytes, urea, Cr, INR, PTT, albumin, iron studies, amoeba titers
- radiologic investigations (including abdominal x-ray to rule out obstruction)
- Meckel’s radionuclide scan

**Management**

- acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
- once stable, endoscopy and/or surgery as indicated

---

**Genetics, Dysmorphisms, and Metabolism**

**Genetics**

**MECHANISMS OF INHERITANCE**

**Mendelian Inheritance**

- disorders caused by mutation of one or both copies of a gene, inherited in one of two patterns:
  - autosomal: encoded by genes on one of 22 pairs of autosomes (chromosomes 1-22)
  - X-linked: encoded by a gene on the X chromosome

**Triplet Repeat Expansions**

- disorder in which trinucleotide repeats in certain genes exceed the normal number and result in altered expression of the gene or production of an abnormal protein (e.g. Fragile X syndrome, spinoocerebellar ataxias, myotonic dystrophy, Huntington disease)

**Imprinting Disorders**

- imprinting: epigenetic process that involves methylation or acetylation of DNA, affecting gene expression
- imprinted genes are expressed differently depending on whether they are inherited from the mother or the father (parent-of-origin gene expression)
- occur when imprinted alleles are silenced (e.g. Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome)

**Mitochondrial Inheritance**

- disorders caused by mutations of the DNA present in mitochondria
- inheritance pattern: mother passes on the defect to all her children; father does not pass on the defect since embryo only receives mitochondria from the mother (in the egg)
METHODS OF GENETIC TESTING
• microarray analysis
  ▪ a microarray is a collection of DNA probes attached to a solid surface
  ▪ microarray analysis can identify small deletions or duplications of genetic material anywhere
    in the genome
  ▪ indicated when there is developmental delay + one or more major malformations
• FISH: usually to identify a gain or loss of chromosomal material
• karyotype: microscopic analysis of all 46 chromosomes with a special stain that shows large
  changes in the number or structure of chromosomes

Genetic Anomalies

Minor and Major Anomalies
• minor anomaly: an unusual anatomic feature that is of no serious medical or cosmetic
  consequence to the patient
• major anomaly: anomaly that creates significant medical, surgical, or cosmetic problems for the
  patient

Mechanism for Anomalies
• malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
• disruption: results from the extrinsic breakdown of, or interference with, an originally normal
  developmental process (e.g. amniotic band disruption sequence)
• deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter
  deformation sequence)
• dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g.
  bone dysplasia)

Multiple Anomalies
• association: non-random occurrence of multiple independent anomalies that appear together
  more than would be predicted by chance but are not believed to have a single etiology (e.g. VACTERL)
• sequence: related anomalies that come from a single initial major anomaly or precipitating
  factor that changes the development of other surrounding or related tissues or structures (e.g.
  Potter sequence)
• syndrome: a pattern of anomalies that occur together and are caused by a single known or
  unknown cause (e.g. Down syndrome)

Approach to the Dysmorphic Child

• genetic disorders are the most common cause of infant death in developed countries

General Approach to the Dysmorphic Child
• Are the anomalies major or minor?
• What is the mechanism underlying the anomaly?
• Do the anomalies fit as part of an association, sequence, or syndrome?

History
• prenatal/obstetrical history (see Obstetrics, OB2) with particular attention to potential
  teratogenic exposures
• complete 3 generation family pedigree: consanguinity, stillbirths, neonatal deaths, specific
  illnesses, intellectual disability, multiple miscarriages, ethnicity
Physical Exam

Investigations
- screening for TORCH infections
- serial photographs if child is older
- x-rays for bony abnormalities
- cytogenetic studies
  - karyotype if recognized syndrome
  - chromosome microarray analysis (array comparative genomic hybridization) if developmental delay with one or more congenital anomalies
  - FISH if microdeletion syndrome or trisomy suspected
- biochemistry: specific enzyme assays
- single gene testing

Management
- prenatal counseling and assessing risk of recurrence
- referral for specialized pediatric or genetic care

Genetic Syndromes

<table>
<thead>
<tr>
<th>Table 18. Common Genetic Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trisomy 21</strong></td>
</tr>
<tr>
<td>Disease</td>
</tr>
<tr>
<td>Incidence</td>
</tr>
<tr>
<td>Most common abnormality of autosomal chromosomes</td>
</tr>
<tr>
<td>Rises with advanced maternal age from 1:1,500 at age 20 to 1:20 by age 45</td>
</tr>
<tr>
<td>Cranium/Brain</td>
</tr>
<tr>
<td>Eyes</td>
</tr>
<tr>
<td>Ears</td>
</tr>
<tr>
<td>Facial Features</td>
</tr>
<tr>
<td>Skeletal/MSK</td>
</tr>
<tr>
<td>Excess nuchal skin</td>
</tr>
<tr>
<td>Cardiac Defect</td>
</tr>
<tr>
<td>GI</td>
</tr>
<tr>
<td>GU</td>
</tr>
</tbody>
</table>
### Table 18. Common Genetic Syndromes (continued)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>CNS</th>
<th>Other Features</th>
<th>Prognosis/Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>Hypotonia at birth</td>
<td>Transverse palmar crease, clinodactyly, and absent middle phalanx of the 5th finger</td>
<td>Prognosis: long-term management per AAP Guidelines (Health Supervision of Children with Down syndrome), recommend chromosomal analysis, CBC, Echo, yearly thyroid test, atlanto-occipital x-ray at 2 yr, sleep study, hearing test, and ophthalmology assessment</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>Hypertonia</td>
<td>SGA</td>
<td>44% die in 1st month 10% survive past 1 yr Profound intellectual disability in survivors</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>Hypo- or hypertonia Seizures, deafness</td>
<td>Single umbilical artery Midline anomalies: scalp, pituitary, palate, heart, umbilicus, anus Rocker-bottom feet</td>
<td>33% die in 1st month, 50% by 2nd month, 90% by 1 yr from FTT Profound intellectual disability in survivors</td>
</tr>
</tbody>
</table>

**Other Features**
- Hypotonia at birth
- Transverse palmar crease, clinodactyly, and absent middle phalanx of the 5th finger
- 1% lifetime risk of leukemia
- Polycythemia
- Hypothyroidism

**Other Features**
- Hypertonia
- Hypo- or hypertonia
- Seizures, deafness
- Severe developmental delay

**Prognosis/Management**
- Profound intellectual disability in survivors
- 44% die in 1st month
- 10% survive past 1 yr

**Other Features**
- 1% lifetime risk of leukemia
- Polycythemia
- Hypothyroidism

**Prognosis/Management**
- 33% die in 1st month
- 50% by 2nd month
- 90% by 1 yr from FTT

**CNS**
- Hypotonia at birth
- Low IQ, developmental delay, hearing problems
- Onset of Alzheimer’s disease in 40s

**Other Features**
- Transverse palmar crease, clinodactyly, and absent middle phalanx of the 5th finger
- 1% lifetime risk of leukemia
- Polycythemia
- Hypothyroidism

**Prognosis/Management**
- Profound intellectual disability in survivors
- 44% die in 1st month
- 10% survive past 1 yr

**Other Features**
- Hypertonia
- Hypo- or hypertonia
- Seizures, deafness
- Severe developmental delay

**Prognosis/Management**
- 33% die in 1st month
- 50% by 2nd month
- 90% by 1 yr from FTT

**CNS**
- Hypotonia at birth
- Low IQ, developmental delay, hearing problems
- Onset of Alzheimer’s disease in 40s

### Table 19. Most Common Sex Chromosome Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Fragile X Syndrome</th>
<th>Klinefelter Syndrome</th>
<th>Turner Syndrome</th>
<th>Noonan Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genotype</strong></td>
<td>X-linked Genetic anticipation CGG trinucleotide repeat on X chromosome measurable by molecular analysis</td>
<td>XXY (most common) XXY, XXXY</td>
<td>45,X (most common)</td>
<td>46,XX or 46,XY Autosomal dominant (not a sex chromosome disorder) with variable expression</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>1:3,600 males, 1:5,000 females</td>
<td>Most common heritable cause of intellectual disability in boys</td>
<td>Increased risk with advanced maternal age</td>
<td>Risk not increased with advanced maternal age</td>
</tr>
<tr>
<td><strong>Phenotype</strong></td>
<td>Overgrowth: prominent jaw, forehead, and nasal bridge with long and thin face, large protuberant ears, macronuchidism, hyperextensibility, and high arched palate Complications: seizures, scoliosis, mitral valve prolapse</td>
<td>Tall, slim, underweight No features prepuberty Postpuberty: male may suffer from developmental delay, long limbs, gynecomastia, lack of facial hair</td>
<td>Short stature, short webbed neck, low posterior hair line, wide carrying angle Broad chest, widely spaced nipples Lymphedema of hands and/or feet, cystic hygroma in newborn with polyhydramnios, lung hypoplasia Coarctation of aorta, bicuspid aortic valve Renal and cardiovascular abnormalities, increased risk of HTN Less severe spectrum with mosaic</td>
<td>Tall, slim, underweight No features prepuberty Postpuberty: male may suffer from developmental delay, long limbs, gynecomastia, lack of facial hair</td>
</tr>
<tr>
<td><strong>IQ and Behavior</strong></td>
<td>Mild to moderate intellectual disability, 20% of affected males have normal IQ ADHD and/or autism Female carriers may show intellectual impairment Male carriers may demonstrate tremor/ataxia syndrome in later life</td>
<td>Mild intellectual disability Behavioral or psychiatric disorders – anxiety, shyness, aggressive behavior, antisocial acts</td>
<td>Mildly deficient to normal intelligence</td>
<td>Moderate intellectual disability in 25% of patients</td>
</tr>
<tr>
<td><strong>Gonad and Reproductive Function</strong></td>
<td>Premutation carrier females at risk of developing premature ovarian failure</td>
<td>Infertility due to hypogonadism/ hypoprospermia</td>
<td>Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics</td>
<td>Delayed puberty</td>
</tr>
<tr>
<td><strong>Diagnosis/Prognosis/Management</strong></td>
<td>Molecular testing of FMR1 gene overamplification of the trinucleotide repeat, length of segment is proportional to severity of clinical phenotype (genetic anticipation)</td>
<td>Increased risk of germ cell tumors and breast cancer Management: testosterone in adolescence</td>
<td>Normal life expectancy if no complications Management: Echo, ECG to screen for cardiac malformation GH therapy for short stature Estrogen replacement at time of puberty for development of secondary sexual characteristics</td>
<td>Molecular testing of PTPN11 gene Management: affected males may require testosterone replacement therapy at puberty Echo, ECG</td>
</tr>
</tbody>
</table>
Table 20. Other Genetic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genotype</th>
<th>Incidence</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DiGeorge Syndrome</td>
<td>Microdeletions of chromosome region 22q11</td>
<td>1:15,000</td>
<td>C: Cyanotic CHD&lt;br&gt;A: Anomalies: craniofacial anomalies typically micrognathia and low set ears&lt;br&gt;T: Thymic hypoplasia: &quot;immunodeficiency&quot; recurrent infections&lt;br&gt;C: Cognitive impairment&lt;br&gt;H: Hypoparathyroidism, hypocalcemia 22q11 microdeletions&lt;br&gt;H: High risk for psychiatric disorders</td>
</tr>
<tr>
<td>Prader-Willi Syndrome</td>
<td>Lack of expression of genes on paternal chromosome 15q11-13 due to deletion, maternal uniparental disomy of chromosome 15, or imprinting defect</td>
<td>1:10,000</td>
<td>H0: Hypotonia and weakness, Hypogonadism, Obsessive Hyperphagia, Obesity&lt;br&gt;H0: Short stature, almond-shaped eyes, small hands and feet with tapering of fingers&lt;br&gt;H0: Developmental delay (variable) Hypopigmentation, type 2 DM</td>
</tr>
<tr>
<td>Angelman Syndrome</td>
<td>Lack of expression of genes on maternal chromosome 15q11-13 due to deletion or inactivation or paternal uniparental disomy</td>
<td>2/3 of children with CHARGE have been found to have a CHD7 mutation on chromosome 8</td>
<td></td>
</tr>
<tr>
<td>CHARGE Syndrome</td>
<td>2/3 of children with CHARGE have been found to have a CHD7 mutation on chromosome 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DUCHENNE MUSCULAR DYSTROPHY

**Epidemiology**
- 1:4,000 males

**Etiology**
- one type of muscular dystrophy characterized by progressive skeletal and cardiac muscle degeneration
- X-linked recessive: 1/3 spontaneous mutations, 2/3 inherited mutations
- missing structural protein (dystrophin) → muscle fiber fragility → fiber breakdown → necrosis and regeneration

**Clinical Presentation**
- proximal muscle weakness by age 3, positive Gower’s sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy

**Diagnosis**
- molecular genetic studies of dystrophin gene (DMD) (first line)
- family history (pedigree analysis)
- increased CK (50-100x normal) and lactate dehydrogenase
- elevated transaminases
- muscle biopsy, EMG

**Management**
- supportive (e.g. physiotherapy, wheelchairs, braces), prevent obesity
- cardiac health monitoring and early intervention
- bone health monitoring and intervention (vitamin D, bisphosphonates)
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

**Complications**
- patient usually wheelchair-bound by 12 yr of age
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or CHF in 2nd-3rd decade

**Metabolic Diseases**
- inherited disorders of metabolism; often autosomal recessive
- infants and older children may present with FTT or developmental delay
- newborn screening includes metabolic disorders
### Table 21. Metabolic Disorders

<table>
<thead>
<tr>
<th>Examples of Conditions</th>
<th>Organic and Amino Acid Disorders</th>
<th>Carbohydrate Disorders</th>
<th>Fatty Acid Disorders</th>
<th>Organelle Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKU</td>
<td></td>
<td>Galactosemia</td>
<td>MCAD deficiency</td>
<td>Mucopeysaccharidosis</td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td></td>
<td>GSDs: von Gierke’s, Pompe’s, Con’s, Andersen, McArdle</td>
<td>Carnitine deficiency</td>
<td>Congenital disorders of glycoseylation</td>
</tr>
<tr>
<td>Homocystinuria</td>
<td></td>
<td></td>
<td></td>
<td>Lyosomal storage diseases: Hurler’s, Niemann-Pick, Tay-Sachs, Gaucher, Fabry, Krabbe</td>
</tr>
<tr>
<td>MSUD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaptonuria</td>
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<td></td>
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<tr>
<td>Urea cycle defects</td>
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<tr>
<td>Urea cycle defects</td>
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</tr>
</tbody>
</table>

#### Clinical Manifestations

<table>
<thead>
<tr>
<th></th>
<th>Hypoglycemia, hyperammonemia, high anion gap (organic acidaemia)</th>
<th>Hypoglycemia, hyperlipidemia (GSD)</th>
<th>Hypoketotic hypoglycemia</th>
<th>Elevated urine oligosaccharides (oligosaccharidoses) and glycosaminoglycans (mucopolysaccharidoses)</th>
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<td>Elevated urine oligosaccharides (oligosaccharidoses) and glycosaminoglycans (mucopolysaccharidoses)</td>
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<tr>
<td></td>
<td>Normoglycemic hyperammonemia, normal anion gap (urea cycle defects)</td>
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</tbody>
</table>

#### Laboratory Findings

<table>
<thead>
<tr>
<th></th>
<th>Hypotonia/hypertonia</th>
<th>Microcephaly, musty odor, eczema, hypopigmentation (PKU)</th>
<th>Infantile cataracts (galactosemia)</th>
<th>Hepatomegaly Hypotonia</th>
<th>Dysmorphic facial features</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Dark urine, pigmented sclerae, arthralgias (alkaptonuria)</td>
<td>Hepatomegaly Muscle weakness/cramping</td>
<td></td>
<td>Macrocephaly (Tay-Sachs, Hurler’s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lens subluxation, marfanoid appearance (homocystinuria)</td>
<td></td>
<td></td>
<td>Hepatosplinomegaly (not Tay-Sachs)</td>
</tr>
</tbody>
</table>

#### Physical Exam

<table>
<thead>
<tr>
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</tr>
</tbody>
</table>

### Initial Investigations
- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, ABGs (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidaemia, fatty acid oxidation defects, and GSDs)
- lactate, ammonium (hyperammonemia with urea cycle defects), plasma Ca\(^{2+}\) and Mg\(^{2+}\)
- routine urinalysis: ketonuria must be investigated
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, plasma amino acid screen, urine organic acids, CSF glycine, free fatty acids (3-β-hydroxybutyrate ratio >4 in fatty acid oxidation defect)
- storage diseases: urine mucopolysaccharide and oligosaccharide screen

### Treatment
- varies according to inborn error of metabolism
- dietary restrictions, supplementation, enzyme replacement therapy, gene therapy, liver transplant, stem cell transplant

### PHENYLKETONURIA

#### Epidemiology
- 1:10,000; autosomal recessive disease

#### Etiology
- deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to build up of toxic metabolites
- mothers who have PKU may have infants with congenital abnormalities

#### Clinical Presentation
- baby is normal at birth, then develops a musty odor, eczema, hypertonia, tremors, and mental retardation
- hypopigmentation due to low tyrosine (fair hair, blue eyes)

#### Management
- PKU screening at birth
- dietary restriction of phenylalanine starting within the first 10 d of life
- duration of dietary restriction controversial – lifelong or until end of puberty; should be resumed during pregnancy to maintain normal phenylalanine levels
GALACTOSEMIA

Epidemiology
• 1:60,000; autosomal recessive disease

Etiology
• most commonly due to deficiency of galactose-1-phosphate uridyltransferase leading to an inability to process lactose/galactose

Clinical Presentation
• signs of liver and renal failure, jaundice, FTT, and cataracts with ingestion of lactose/galactose

Management
• elimination of galactose from the diet (e.g. dairy, breast milk)
• most infants are fed a soy-based diet

Complications
• increased risk of sepsis, especially E. coli
• if the diagnosis is not made at birth, liver and brain damage may become irreversible

Hematology

Approach to Anemia

Physiologic Anemia
• high Hb (>170 g/L) and reticulocyte count at birth is caused by a hypoxic environment in utero
• after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 wk of life, there is virtually no erythropoiesis due to new O₂ rich environment), and increasing blood volume secondary to growth
• lowest levels about 100 g/L at 8-12 wk age (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
• no treatment usually required

Iron Deficiency Anemia
• most common cause of childhood anemia
• full term infants exhaust iron reserves by 6 mo of age
• premature infants have lower reserves, therefore exhausted by 2-3 mo of age
• common diagnosis between 6 mo-3 yr and 11-17 yr due to periods of rapid growth and increased iron requirements; adolescents also have poor diet and menstrual losses

Etiology
• children at risk (premature, LBW, low SES, First Nations, etc.)
• dietary risk factors: whole cow milk in first year of life
• age >6 mo: <2 servings/d of iron-fortified cereal, red meat, or legumes
• age <12 mo: use of low-iron formula (<10 mg/L), primary diet of cow, goat, or soy milk
• age 1-5 yr: >16-20 oz/d of non-fortified milk
• blood loss
  ▪ iatrogenic: repeated blood sampling (especially in hospitalized neonates)
  ▪ allergic: cow milk protein-induced colitis

Clinical Manifestation
• usually asymptomatic until marked anemia, pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur, angular cheilitis, koilonychie

Investigations
• CBC: low Hb, MCV, and MCH, reticulocyte count normal or high (absolute number low)
• Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
  ▪ ratio <13 suggests thalassemia; ratio >13 suggests iron deficiency
• blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikilocytosis
• iron studies: low ferritin, other (low iron, high total iron binding capacity, high transferrin, low transferrin saturation)
• initial therapy: trial of iron

Prevention
• breastfed term infants: begin iron supplementation (1 mg/kg/d) at 4-6 mo, continuing until able to eat ≥2 feeds/d of iron-rich foods
• non-breastfed (<50% of diet) term infants: give iron-fortified formula from birth
• premature infants: give iron supplements from 1 mo through to 1 yr of age
• no cow's milk until 9-12 mo, early introduction of red meat and iron-rich vegetables: total daily iron should be 11 mg (age 6-12 mo), 7 mg (age 1-3 yr)
• universal screening of Hb levels recommended at 9 mo

Management
• encourage diverse, balanced diet, limit homogenized milk to 16-20 oz/d
• oral iron therapy: 6 mg/kg/d elemental iron, divided bid to tid, for 3 mo
  ▪ increased reticulocyte count in 2-3 d (peaks day 5-7)
  ▪ increased hemoglobin in 4-30 d
  ▪ repletion of iron stores in 1-3 mo
  ▪ repeat hemoglobin levels after 1 mo of treatment
• poor response to oral iron therapy: non-compliance, medication intolerance, ongoing blood loss, IBD, celiac disease, incorrect diagnosis

Complications
• can cause irreversible effects on development if untreated (behavioral and intellectual deficiencies)
• angular cheilitis, glossitis, koilonychia (spoon nails)

**Vitamin K Deficiency**

• HDNB due to relative deficiencies of vitamin K-dependent coagulation factors
  ▪ generalized bleeding; GI/intracranial hemorrhage
• IM injection at birth, can also be given orally (3 doses: at birth, 2-4 wk, 6-8 wk) but infants at higher risk of HDNB
• reason for administration at birth
  ▪ human milk contains small amounts of vitamin K, and infants require ingestion of large volumes of human milk to promote GI bacterial colonization
  ▪ until few days after birth, susceptible to vitamin K deficiency

**Anemia of Chronic Disease**

• see Hematology, H16

**Sickle Cell Disease**

• see Hematology, H21

Presentation
• newborn screen
• clinical disease presents at 5-6 mo of age after fall in fetal Hb

8% of African Americans carry the HbS trait, 0.2% have the disease

Heterozygotes (trait) are relatively malaria-resistant
• anemia, fever (medical emergency – infection is leading cause of death in SCD), jaundice, splenomegaly, crisis (dactylitis is often the first presentation)
• sickle cell trait: asymptomatic (may have microscopic hematuria and later isothenuria)
• vaso-occlusive crisis
  ▪ due to obstruction of blood vessels by rigid, sickled cells → tissue hypoxia → cell death; presents as fever and pain in any organ; most commonly in long bones of arms and legs, chest, abdomen, CNS (stroke), dactylitis (in young children), priapism
  ▪ acute chest crisis: fever, chest pain, progressive respiratory distress, increased WBC count, pulmonary infiltrates
  ▪ aplastic crisis: depression of erythropoiesis (decreased reticulocyte count to <1%, decreased Hb), generally associated with infection (especially parvovirus B19)
• acute splenic sequestration: sudden, massive pooling of red cells in spleen, splenomegaly, tender spleen, acute fall in hemoglobin, shock, increased reticulocyte count; splenic dysfunction (functional asplenia) by 5 yr of age secondary to auto-infarction; risk for sepsis from encapsulated organisms
• risk of osteomyelitis with *Salmonella*

Other Manifestations
• long-term complications: growth delay, bony abnormalities (e.g. avascular necrosis of femoral head), gallstones, retinopathy, restrictive lung disease (screen with PFTs), cardiomyopathy (screen with Echo), and pulmonary HTN

Management
• acute crises
  ▪ admit for supportive and symptomatic treatment
  ▪ fluids (1.5x maintenance; 1x maintenance only if in chest crisis), analgesia (opioid, multi-modal), antibiotics (e.g. 3rd generation cephalosporins), incentive spirometry and ambulation to decrease risk of chest crisis
  ▪ straight transfusions for symptomatic/significant anemia, evolving chest crisis
  ▪ RBC exchange transfusion for impending stroke, severe chest crisis, persistent priapism
  ▪ O2 if respiratory distress or chest crisis (with incentive spirometry)
  ▪ CBC, reticulocyte counts, cultures if febrile, CXR, or LP if indicated
• chronic
  ▪ early aggressive treatment of infections, prophylactic antibiotics (daily oral penicillin)
  ▪ pneumococcal, meningococcal, hepatitis B, Hib, and influenza vaccines
  ▪ folate supplementation
  ▪ hydroxyurea if frequent crises, history of acute chest syndrome (raises HbF level)
  ▪ transcranial Doppler to assess risk of stroke
  ▪ chronic transfusion program if history of stroke or abnormal transcranial Doppler
  ▪ genetic counseling and education
  ▪ annual fundoscopic exam (after 10 yr old)
  ▪ bi-annual screening for pulmonary HTN (after 12 yr old)
  ▪ bi-annual chemistry and urinanalysis to monitor organ dysfunction

**Thalassemia**
• see *Hematology*, H19

**Hereditary Spherocytosis**
• see *Hematology*, H23

**Glucose-6-Phosphate Dehydrogenase Deficiency**
• see *Hematology*, H23

G6PD deficiency protects against parasitism of RBCs (i.e. malaria)
Bleeding Disorders

• see Hematology, H27

Table 22. Evaluation of Abnormal Bruising/Bleeding

<table>
<thead>
<tr>
<th>PFA</th>
<th>PT</th>
<th>PTT</th>
<th>VIII:C</th>
<th>vWF</th>
<th>Platelets</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>von Willebrand Disease</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DIC</td>
<td>N or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>Vitamin K Deficiency</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; PFA = platelet function assay; VIII:C = Factor VIII coagulant activity; vWF = von Willebrand’s factor;

Immune Thrombocytopenic Purpura

Epidemiology
• most common cause of thrombocytopenia in childhood
• peak age: 2-6 yr, M=F
• incidence 5:100,000 children per yr

Etiology
• caused by autoantibodies that bind to platelet membranes → Fc-receptor mediated splenic uptake → destruction of platelets

Clinical Presentation
• 50% present 1-3 wk after viral illness (URTI, chicken pox)
• sudden onset of petechiae, purpura, epistaxis in an otherwise well child
• clinically significant bleed in only 3% (severe bleed more likely with platelet count <10) with <0.5% risk of intracranial bleed
• no lymphadenopathy, no hepatosplenomegaly
• labs: thrombocytopenia with normal RBC, WBC
• bone marrow aspirate only if atypical presentation (≥1 cell line abnormal, hepatosplenomegaly)
• differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), autoimmune (SLE, ALPS)

Management
• observation vs. pharmacologic intervention highly debated; spontaneous recovery in >70% of cases within 3 mo
• treatment with IVIg or prednisone if mucosal or internal bleeding, platelets <10, or at risk of significant bleeding (surgery, dental procedure, concomitant vasculitis or coagulopathy)
• life-threatening bleed: additional platelet transfusion ± emergency spleenectomy
• persistent (>3-12 mo) or chronic (>12 mo): re-evaluate; treat if symptoms persist
• supportive: avoid contact sports and ASA/NSAIDs

Hemophilia

• see Hematology, H31

von Willebrand’s Disease

• see Hematology, H30
Oncology

- cancer is the second most common cause of death after injuries in children after 1 yr of age
- cause is rarely known, but increased risk for children with: chromosomal syndromes (e.g. Trisomy 21), prior malignancy, neurocutaneous syndromes, immunodeficiency syndromes, family history, exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (40%), followed by brain tumors (20%), and lymphomas (15%)
- some malignancies are more prevalent in certain age groups:
  - newborns: neuroblastoma, Wilms' tumor, retinoblastoma
  - infancy and childhood: leukemia, neuroblastoma, Wilms' tumor, retinoblastoma
  - adolescence: lymphoma, gonadal tumors, bone tumors
- unique treatment considerations in pediatrics because radiation, chemotherapy, and surgery can impact growth and development, endocrine function, and fertility
- good prognosis: treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers (>80%)

Lymphadenopathy

Clinical Presentations
- features of malignant lymphadenopathy: firm, discrete, non-tender, enlarging, immobile ± suspicious mass/imaging findings ± constitutional symptoms
- fluctuance, warmth, or tenderness are more suggestive of benign nodes (infection)

Differential Diagnosis
- infection
  - viral: URTI, EBV, CMV, adenovirus, HIV
  - bacterial: S. aureus, GAS, anaerobes, Mycobacterium (e.g. TB), cat scratch disease (Bartonella)
  - other: fungal, protozoan, Rickettsia
- autoimmune: rheumatoid arthritis, SLE, serum sickness
- malignancy: lymphoma, leukemia, metastatic solid tumors
- storage diseases: Niemann-Pick, Gaucher's
- other: sarcoidosis, Kawasaki disease, histiocytoses

Investigations
- generalized lymphadenopathy
  - CBC and differential, blood culture
  - uric acid, LDH
  - ANA, RF, ESR
  - EBV/CMV/HIV serology
  - toxoplasma titer
  - fungal serology
  - CXR
  - TB tests
  - biopsy
- regional lymphadenopathy
  - period of observation if asymptomatic
  - trial of oral antibiotics
  - ultrasound
  - biopsy (especially if persistent >6 wk and/or constitutional symptoms)

Leukemia

- see Hematology, H37, H40, H43, H48

Epidemiology
- mean age of diagnosis 2-5 yr but can occur at any age
- heterogeneous group of diseases
  - ALL (80%)
  - AML (15%)
  - CML (<5%)
- children with DS are 15x more likely to develop leukemia

Clinical Presentation
- infiltration of leukemic cells into bone marrow results in bone pain and bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in lymphadenopathy, hepatosplenomegaly, CNS manifestations, testicular disease
- fever, fatigue, weight loss, bruising, and easy bleeding
hyperleukocytosis (total WBC $>10.0 \times 10^9/dL$) is a medical emergency
  - presents clinically with respiratory or neurological distress caused by hyperviscosity of blood and leukostasis
  - risk of ICH, pulmonary leukostasis syndrome, tumor lysis syndrome
  - management: fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes)

Management
- combination chemotherapy using non-cross resistant chemotherapy agents, allogeneic stem cell transplantation for high-grade or recurrent disease
- supportive care and management of treatment complications
  - febrile neutropenia: see Infectious Diseases, ID46
  - tumor lysis syndrome: see Hematology, H52

Prognosis
- 80-90% 5 yr event-free survival for ALL, 50-60% 5 yr survival for AML
- patients are stratified into standard risk and high risk based on WBC and age; other prognostic factors include presence of CNS/testicular disease, immunophenotype, cytogenetics, and initial response to therapy (most important prognostic variable)

Lymphoma

- see Hematology, H44

Epidemiology
- Hodgkin lymphoma: incidence is bimodal, peaks at ages 15-34 and >50 yr old
- non-Hodgkin lymphoma: incidence peaks at 7-11 yr

Clinical Presentation
- Hodgkin lymphoma
  - most common presentation is persistent, painless, firm, cervical, or supraclavicular lymphadenopathy
  - can present as persistent cough or dyspnea (secondary to mediastinal mass) or less commonly as splenomegaly, axillary, or inguinal lymphadenopathy
  - constitutional symptoms in 30% of children
- non-Hodgkin lymphoma
  - generally categorized into lymphoblastic, large cell, and Burkitt’s/Burkitt’s-like lymphoma
  - rapidly growing tumor with distant metastases (unlike adult non-Hodgkin lymphoma)
  - signs and symptoms related to disease site: most commonly abdomen, chest (mediastinal mass), head and neck region

Management
- Hodgkin lymphoma
  - combination chemotherapy and radiation
  - aimed at limiting cumulative doses of anthracyclines (toxic to heart) and alkylators (risk of second malignancy, infertility) and limiting dose and field of radiation
  - increasing role for use of PET scanning to assess early disease response and plan therapy
- non-Hodgkin lymphoma
  - combination chemotherapy
  - no added benefit of radiation in pediatric protocols

Prognosis
- Hodgkin lymphoma: >90% 5 yr survival
- non-Hodgkin lymphoma: 75-90% 5 yr survival

Brain Tumors

- see Neurosurgery, NS10, NS38

Wilms’ Tumor (Nephroblastoma)

Epidemiology
- usually diagnosed between 2-5 yr M=F
  - most common primary renal neoplasm of childhood
  - 5-10% of cases both kidneys are affected (simultaneously or in sequence)
Differential Diagnosis
- hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma

Clinical Presentation
- 80% present with asymptomatic, unilateral abdominal mass
- may also present with HTN, gross hematuria, abdominal pain, vomiting
- may have pulmonary metastases at time of diagnosis (respiratory symptoms)

Associated Congenital Abnormalities
- WAGR syndrome (Wilms' tumor, Aniridia, Genital anomalies, mental Retardation) with 11p13 deletion
- Beckwith-Wiedemann syndrome
  - characterized by enlargement of body organs (especially tongue), hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
  - also at increased risk for developing hepatoblastoma, and less commonly adrenocortical tumors, neuroblastomas, and rhabdomyosarcomas
- Denys-Drash syndrome: characterized by gonadal dysgenesis and nephropathy leading to renal failure

Management
- staging ± nephrectomy
- chemotherapy, radiation for higher stages

Prognosis
- 90% long-term survival

**Neuroblastoma**

Epidemiology
- most common cancer occurring in first year of life
- neural crest cell tumor arising from sympathetic tissues (neuroblasts)

Clinical Presentation
- can originate from any site in sympathetic nervous system, presenting as mass in neck, chest, or abdomen (most common site is adrenal gland)
- signs and symptoms of disease vary with location of tumor
  - thoracic: dyspnea, Horner's syndrome
  - abdomen: palpable mass
  - spinal cord compression
- metastases are common at presentation (>50% present with advanced stage disease):
  - usually to bone or bone marrow (presents as bone pain, limp)
  - can also present with periorbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, "blueberry muffin" skin nodules
  - paraneoplastic: HTN, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from vasoactive intestinal peptide secretion), opsomyoclonus
- diagnostic criteria (either of the following)
  - unequivocal histologic diagnosis from tumor tissue biopsy
  - evidence of metastasis to bone marrow ("rosettes") on aspirate analysis, with concomitant elevation of urine or serum catecholamine metabolite (VMA, HVA) levels

Management
- depends on prognostic factors and may include combination of: surgery, radiation, chemotherapy, autologous stem cell transplantation, immunotherapy

Prognosis
- prognosis is often poor due to late detection
- good prognostic factors
  - "age and stage" are important determinants of better outcome: 12-18 mo, stage I, II, IV-S disease ("S" designates a "Special" classification only pertaining to infants)
  - primary site: posterior mediastinum and neck
  - low serum ferritin
  - specific histology
  - tumor cell markers: aneuploidy, absent MYCN oncogene amplification

**Bone Tumors**
- see Orthopedics, OR43
Infectious Diseases

Fever

Definition
- fever: no generally accepted definition, a practical definition is >100.4°F/38°C oral or rectal
- fever without a source/focus: acute febrile illness (typically <10 d duration) with no cause of fever even after careful history and physical
- fever of unknown origin: daily or intermittent fevers for at least 2 consecutive weeks of uncertain cause after careful history and physical, and initial laboratory assessment

Etiology
- infectious: anatomic approach (CNS, ears, upper and lower respiratory tract, GI, GU, skin, soft tissue, bones and joints, etc.)
- inflammatory: mainly autoimmune (Kawasaki disease, JIA, IBD, SLE, etc.)
- malignancy: childhood cancers (leukemia, lymphoma, neuroblastoma, etc.)
- miscellaneous: dehydration, drugs and toxins, post-immunization, familial dysautonomia, factitious disorder, etc.

Diagnosis
- history: duration, height and pattern of fever, associated symptoms, exposures, constitutional symptoms, recent antipyretic use, ethnic or genetic background, day care, sick contacts, travel, tick bites
- physical exam: toxic vs. non-toxic, vitals, growth, complete exam of the skin, HEENT, chest, abdomen, lymph nodes, genitalia
- investigations: guided by history, physical exam, and clinical suspicion

Evaluation of Neonates and Infants with Fever
- several protocols exist that attempt to identify neonates and young infants at low risk of serious bacterial infection (e.g. Rochester criteria)
  - such protocols are not as sensitive in the 1-28 d age group; therefore, febrile neonates should be considered high risk regardless of clinical presentation and laboratory findings

Management
- admit to hospital if appropriate
- treat the source if known
- replace fluid losses (e.g. from vomiting, diarrhea, etc.); maintenance fluid needs are higher in febrile child
- reassure parents that most fevers are benign and self-limited
- antipyretics (acetaminophen and/or ibuprofen) are not necessary in most cases, but can be given if child is uncomfortable

Figure 11. Approach to the febrile child

Rochester Criteria – Developed to Identify Infants ≤60 d of Age with Fever at Low Risk of Serious Bacterial Infection

<table>
<thead>
<tr>
<th>Cliniy</th>
<th>WBC Count</th>
<th>Bands</th>
<th>Urinalysis</th>
<th>Stool (if diarhea)</th>
<th>Past Health</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well</td>
<td>5-15 x 10^9/L</td>
<td>&lt;1.5 x 10^9/L</td>
<td>&lt;10 WBC/HPF</td>
<td>5 WBC/HPF</td>
<td>Home with/before mom</td>
<td>&lt;28 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28-90 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 mo-3 yrs</td>
</tr>
</tbody>
</table>

NOTES
1. Full Septic Workup (SWU) – blood C&S, CBC and differential, urine R&M, C&S, LP, CXR if respiratory symptoms, stool C&S if GI symptoms
2. Follow-up is crucial – if adequate follow-up is not assured, a more aggressive diagnostic and therapeutic approach may be indicated
3. Low-risk (Rochester) criteria
4. Considerable practice variation exists in terms of empiric antibiotic treatment
5. Important principles – the younger the child, the greater the difficulty to clinically assess the degree of illness
Acute Otitis Media

Definition
All of
1. presence of middle ear effusion
2. presence of middle ear inflammation
3. acute onset of symptoms of middle ear effusion and inflammation

Epidemiology
• 60-70% of children have at least 1 episode of AOM before 3 yr of age
• 18 mo-6 yr most common age group
• peak incidence January to April
• one third of children have had ≥3 episodes by age 3

Etiology
• S. pneumoniae: 32% of cases (incidence decreasing due to pneumococcus vaccine)
• H. influenzae (non-typeable): 28% of cases
• M. catarrhalis: 14% of cases
• S. aureus and S. pyogenes (all β-lactamase producing)
• anaerobes (newborns)
• Gram-negative enterics (infants)
• viral

Predisposing Factors
• Eustachian tube dysfunction/obstruction
  ▪ swelling of tubal mucosa: URTI, allergic rhinitis, chronic rhinosinusitis
  ▪ obstruction/infiltration of Eustachian tube ostium: adenoid hypertrophy (not due to obstruction but by maintaining a source of infection), barotrauma (sudden changes in air pressure)
  ▪ inadequate tensor palati function: cleft palate (even after repair)
  ▪ abnormal Eustachian tube: DS (horizontal position of Eustachian tube), Crouzon syndrome, cleft palate, and Apert syndrome
• disruption of action of
  ▪ cilia of Eustachian tube: Kartagener's syndrome
• mucus secreting cells
• capillary network that provides humoral factors, neutrophils, phagocytic cells
• immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, CF

Risk Factors
• bottle feeding, pacifier use
• second-hand smoke
• crowded living conditions (day care/group child care facilities) or sick contacts
• male
• family history

Pathogenesis
• obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant "edema of mucosa with exudate/effusion to middle ear mucosa)

Clinical Features
• triad of otalgia, fever (especially in younger children), and conductive hearing loss
• rarely tinnitus, vertigo, and/or facial nerve paralysis
• otorrhea if tympanic membrane perforated
• infants/toddlers: ear-tugging (this alone is not a good indicator of pathology), hearing loss, balance disturbances (rare), irritable, poor sleeping, vomiting and diarrhea, anorexia
• otoscopy of TM: hyperemia, bulging, pus may be seen behind TM, loss of landmarks (e.g. handle and long process of malleus not visible)

Diagnosis and Management
• Diagnose AOM if
  • moderate to severe bulging of TM or new onset of otorrhea not due to acute otitis externa
  • mild bulging of tympanic membrane and recent (<48 h) ear pain or intense erythema of TM
  • do not diagnose AOM if no middle ear effusion (based on pneumatic otoscopy or tympanometry)
  • antibiotic treatment hastens resolution: 10 d course
  • 1st line
    ▪ amoxicillin 75-90 mg/kg/d divided into two doses: safe, effective, and inexpensive
    ▪ if penicillin allergic: macrolide (clarithromycin, azithromycin – high resistance), trimethoprim-sulphamethoxazole (Bactrim®)

Recommendations
• Recommend pneumococcal conjugate vaccine to all children according to vaccination schedule.

Strong Recommendations
• Management of AOM should include an assessment of pain; if pain is present, the clinician should recommend treatment to reduce pain.
• Severe AOM in young children:
  • Prescribe antibiotic therapy for AOM (bilateral or unilateral) in children 6 mo and older with severe signs or symptoms (i.e. moderate or severe otalgia in otalgia for at least 48 h or temperature 102.2°F [39°C] or higher).
• Recommended pneumococcal conjugate vaccine to all children according to vaccination schedule.
  • Diagnose AOM in children who present with moderate to severe bulging of the TM or new onset of otorhea not due to acute otitis externa.
  • Diagnose AOM in children who present with mild bulging of the TM and recent (<48 h) onset of ear pain (tugging, tugging of the ear in a nonverbal child) or intense erythema of the TM.
  • Non-severe AOM in young children:
    • Prescribe antibiotic therapy for bilateral AOM in children 6 mo through 23 mo of age without severe signs or symptoms (i.e. mild otalgia for less than 48 h and temperature less than 102.2°F [39°C]).
    • Either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision making with the parent(s)/ caregiver(s) for unilateral AOM in children 6-23 mo of age or bilateral or unilateral AOM in children ≥24 mo without severe signs or symptoms; when observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48-72 h of onset of symptoms.
  • Prescribe amoxicillin for AOM when a decision to treat with antibiotics has been made and the child has not received amoxicillin in the past 30 d or the child does not have concurrent purulent conjunctivitis or the child is not allergic to penicillin.
  • Prescribe an antibiotic with additional β-lactamase coverage for AOM when a decision to treat with antibiotics has been made and the child has received amoxicillin in the last 30 d or has concurrent purulent conjunctivitis, or has a history of recurrent AOM unresponsive to amoxicillin.
  • Reassess the patient if the caregiver reports that the child’s symptoms have worsened or failed to respond to the initial antibiotic treatment within 48-72 h and determine whether a change in therapy is needed.
  • Do not prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM.
  • Recommend annual influenza vaccine to all children according to vaccination schedule.
  • Encourage exclusive breastfeeding for at least 6 mo.
  • Encourage avoidance of tobacco smoke exposure.

Option
• Offer tympanostomy tubes for recurrent AOM (3 episodes in 6 mo or 4 episodes in 1 yr with 1 episode in the preceding 6 mo).

References
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Pediatrics 2011;128:e64-699

JAMA
Clinical Assessment of AOM in Pediatrics
Clinical Assessment of AOM in Pediatrics
Clinical Assessment of AOM in Pediatrics
amoxicillin-clavulanic acid (Augmentin®)
cephalosporins: cefuroxime axetil (Zinacef®), ceftriaxone (Rocephin®), cefaclor (Ceclor®), cefixime (Suprax®)
AOM deemed unresponsive if clinical signs/symptoms and otoscopic findings persist beyond 48 h of antibiotic treatment
symptomatic therapy
antipyretics/analgesics (e.g. acetaminophen)
decongestants: may relieve nasal congestion but does not treat AOM
prevention
parent education about risk factors
antibiotic prophylaxis: amoxicillin or macrolide shown effective at half therapeutic dose
pneumococcal and influenza vaccine
surgery
choice of surgical therapy for recurrent AOM depends on whether local factors (Eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinusitis) are responsible

Complications
extracranial: hearing loss and speech delay (secondary to persistent middle ear effusion), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
intracranial: meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis

Otitis Media with Effusion

Definition
presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology
most common cause of pediatric hearing loss
not exclusively a pediatric disease
follows AOM frequently in children
middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10%

Risk Factors
same as AOM

Clinical Features
conductive hearing loss ± tinnitus
fullness – blocked ear
± pain, low grade fever
otoscopy of TM

discoloration – amber or dull gray with "glue" ear
meniscus fluid level behind TM
air bubbles
retraction pockets/TM atelectasis
most reliable finding with pneumatic otoscopy is immobility

Treatment
expectant: 90% resolve by 3 mo
document hearing loss with audiogram (see Otolaryngology Figure 16B and Figure 17B, OT10)
no statistical proof that antihistamines, decongestants, antibiotics clear disease faster
surgery: myringotomy ± ventilation tubes ± adenoidectomy (if enlarged or on insertion of second set of tubes after first set falls out)
ventilation tubes to equalize pressure and drain ear

Complications of OME
hearing loss, speech delay, learning problems in young children
chronic mastoiditis
ossicular erosion
cholesteatoma especially when retraction pockets involve pars flaccida
retraction of tympanic membrane, atelectasis, ossicular fixation

Gastroenteritis
see Gastroenterology, P36

HIV Infection
see Infectious Diseases, ID29
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen(s)</th>
<th>Incubation Period</th>
<th>Communicability</th>
<th>Mode of Transmission</th>
<th>Rash</th>
<th>Associated Features</th>
<th>Management</th>
<th>Outcomes and Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema Infectiosum (i.e. Fifth Disease)</td>
<td>Parvovirus B19</td>
<td>4-14 d</td>
<td>Low risk of transmission once symptomatic</td>
<td>Respiratory secretions or infected blood</td>
<td>Appearance: uniform, erythematous maculopapular 'lacy' rash Timing: 10-17 d after symptoms (immune response) Distribution: bilateral cheeks ('slapped cheeks') with circumoral sparing; may affect trunk and extremities</td>
<td>Initial 7-10 d of flu-like illness and fever Rash may be warm, non-tender, and pruritic Less common presentations include 'gloves and socks syndrome' or STAR complex (sore throat, arthritis, rash)</td>
<td>Supportive</td>
<td>Rash fades over days to week, but may reappear months later with sunlight, exercise Aplastic crisis</td>
</tr>
<tr>
<td>Gianotti-Crosti Syndrome (i.e. Papular Acrodermatitis)</td>
<td>EBV and Hep B (majority)</td>
<td>Variable</td>
<td>None</td>
<td>—</td>
<td>Appearance: asymptomatic symmetric papules Distribution: face, cheeks, exterior surfaces of the extremities, spares trunk</td>
<td>Viral prodrome May have lymphadenopathy and/or hepatosplenomegaly</td>
<td>Supportive</td>
<td>Resolves in 3-12 wk</td>
</tr>
<tr>
<td>Hand, Foot, and Mouth Disease</td>
<td>Coxsackie group A</td>
<td>3-5 d</td>
<td>Likely 1-7 d after symptoms but may be up to months</td>
<td>Direct and indirect contact with infected bodily fluids, fecal-oral</td>
<td>Appearance: vesicles and pustules on an erythematous base Distribution: acral</td>
<td>Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue)</td>
<td>Supportive</td>
<td>Mainly dehydration</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>HSV 1,2</td>
<td>1-26 d</td>
<td></td>
<td>Direct contact, often through saliva for HSV-1 and sexual contact for HSV-2</td>
<td>Grouped vesicles on an erythematous base</td>
<td>Enanthem: vesicles/erosions in the ANTERIOR oral cavity (buccal mucosa, tongue) May present with herpetic whitlow (autoinoculation)</td>
<td>Mainly supportive Consider oral or topical antivirals</td>
<td>Local: secondary skin infections, keratitis, gingivostomatitis CNS: encephalitis Disseminated hepatitis, DIC Eczema herpeticum</td>
</tr>
<tr>
<td>Kawasaki Disease</td>
<td>See P96</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>Morbillivirus</td>
<td>8-13 d</td>
<td>4 d before and after rash</td>
<td>Airborne</td>
<td>Appearance: erythematous maculopapular Timing: 3 d after start of symptoms Distribution: starts at hairline and spreads downwards with sparing of palms and soles</td>
<td>Prodome of cough, coryza, conjunctivitis (3 Cs) Enanthem: Koplik’s spots 1-2 d before rash Desquamation Positive serology for measles IgM</td>
<td>Infected: supportive Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure Respiratory isolation, report to Public Health Prevention: MMR vaccine</td>
<td>Secondary bacterial infections: AOM, sinusitis, pneumonia Encephalitis Rare: myocarditis, pericarditis, thrombocytopenia, Stevens-Johnson syndrome, GN, subacute sclerosing panencephalitis</td>
</tr>
<tr>
<td>Disease</td>
<td>Pathogen(s)</td>
<td>Incubation Period</td>
<td>Communicability</td>
<td>Mode of Transmission</td>
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</tr>
<tr>
<td><strong>Non-Specific Enteroviral Exanthems</strong></td>
<td>Enteroviruses</td>
<td>Variable</td>
<td>Variable</td>
<td>Direct and indirect contact with infected bodily fluids</td>
<td>Polymorphous rash (macules, papules, vesicles, petechiae, urticaria)</td>
<td>Systemic involvement is rare, but possible</td>
<td>Supportive Diagnosis confirmed using viral cultures (NP and rectal swabs)</td>
<td>Self-limiting</td>
</tr>
<tr>
<td><strong>Roseola</strong></td>
<td>HHV 6</td>
<td>5-15 d</td>
<td>Unknown</td>
<td>—</td>
<td>Appearance: blanching, pink, maculopapular Timing: appears once fever subsides Distribution: starts at the neck and trunk and spreads to the face and extremities</td>
<td>High grade fever Common: irritability, anorexia, lymphadenopathy, erythematous TM and pharynx, Nagayama spots (erythematous papules on soft palate and uvula), Less common: cough, coryza, bulging fontanelles</td>
<td>Supportive</td>
<td>CNS: febrile seizures (10-25%), aseptic meningitis Thrombocytopenia</td>
</tr>
<tr>
<td><strong>Rubella</strong></td>
<td>Rubivirus</td>
<td>14-21 d</td>
<td>7 d before and after eruptions</td>
<td>Droplet</td>
<td>Appearance: pink, maculopapular Timing: 1-5 d after start of symptoms Distribution: starts on face and spreads to neck and trunk</td>
<td>Prodrome of low grade fever and occipital/rearauricular nodes STAR complex (sore throat, arthritis, rash), Positive serology for rubella IgM</td>
<td>Infected: supportive Prevention: MMR vaccine Report to Public Health</td>
<td>Excellent prognosis with acquired disease Arthritis may last days to weeks Encephalitis Irreversible defects in congenitally infected patients (i.e. congenital rubella syndrome)</td>
</tr>
<tr>
<td><strong>Scarlet Fever</strong></td>
<td>See P60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Varicella</strong></td>
<td>Varicella zoster virus</td>
<td>0-21 d</td>
<td>1-2 d pre-eruptions and 5 d post-eruption</td>
<td>Mainly airborne, but also through direct contact with vesicle fluid Timing: 1-3 d after start of symptoms Distribution: generalized</td>
<td>Appearance: groups of skin lesions, polymorphic, from macules to papules to vesicles to crusts</td>
<td>Significant pruritis Enanthem: vesicular lesions which may become pustular or ulcerate</td>
<td>Supportive Avoid salicylates (due to risk of Reye syndrome) Consider antivirals Respiratory and contact isolation, report to Public Health Prevention: varicella vaccine</td>
<td>Skin: bacterial superinfection, necrotizing fasciitis CNS: acute encephalitis and cerebellar ataxia Systemic: hepatitis, DIC Congenital varicella syndrome if intrapartum infection</td>
</tr>
</tbody>
</table>
Infectious Mononucleosis

Definition
• systemic viral infection caused by EBV with multivisceral involvement; often called "the great imitator"

Epidemiology
• peak incidence between 15-19 yr old
• ~50% of children in developed countries have a primary EBV infection by 5 yr old, but <10% of children develop clinical infection

Etiology
• EBV: a member of herpesviridae
• transmission is mainly through infected saliva ("kissing disease") and sexual activity (less commonly); incubation period of 1-2 mo

Risk Factors
• infectious contacts, sexually active, multiple sexual partners in the past

History
• prodrome: 2-3 d of malaise, anorexia
• infants and young children: often asymptomatic or mild disease
• older children and adolescents: malaise, fatigue, fever, sore throat, abdominal pain (often LUQ), headache, myalgia

Physical Exam
• classic triad: febrile, generalized non-tender lymphadenopathy, pharyngitis/tonsillitis (exudative)
• ± hepatosplenomegaly
• ± periorbital edema, ± rash (urticarial, maculopapular, or petechial) – more common after inappropriate treatment with β-lactam antibiotics
• any "-itis" (including arthritis, hepatitis, nephritis, myocarditis, meningitis, encephalitis, etc.)

Investigations
• heterophil antibody test (Monospot® test)
  ▪ 85% sensitive in adults and older children, but only 50% sensitive if <4 yr of age
  ▪ false positive results with HIV, SLE, lymphoma, rubella, parvovirus
• EBV titers
• CBC and differential, blood smear: atypical lymphocytes, lymphocytosis, Downey cells ± anemia ± thrombocytopenia
• throat culture to rule out streptococcal pharyngitis

Management
• supportive: adequate rest, hydration, saline gargles, and analgesics for sore throat
• splenic enlargement is often not clinically apparent so all patients should avoid contact sports for 6-8 wk
• if airway obstruction secondary to nodal and/or tonsillar enlargement is present (especially younger children), admit for steroid therapy
• acyclovir does NOT reduce duration of symptoms or result in earlier return to school/work

Prognosis
• most acute symptoms resolve in 1-2 wk, though fatigue may last for months
• short-term complications: splenic rupture, Guillain-Barré syndrome

Infectious Pharyngitis/Tonsillitis

Definition
• inflammation of the pharynx, especially the tonsils if present, causing a sore throat

Etiology
• viral (~80%): adenoviruses, enteroviruses, coxsackie, upper respiratory tract viruses, EBV, CMV
• bacterial (~20%): mainly GAS, M. pneumoniae (older children), N. gonorrhoeae (sexually active), C. diphtheriae (unvaccinated)
• fungal: Candida

Epidemiology
• season: GAS pharyngitis more common in late winter or early spring; viral all year long
• age: GAS pharyngitis peak incidence at 5-12 yr of age and uncommon <3 yr; viral pharyngitis affects all ages
History
• GAS: sore throat (may be severe), fever, malaise, headache, abdominal pain, N/V, absence of other URTI symptoms
• viral: sore throat (often mild), conjunctivitis, cough, rhinorrhea, hoarseness, diarrhea, flu-like symptoms (fever, malaise, myalgias)

Physical Exam
• GAS: febrile, pharyngeal/tonsillar erythema and exudates, enlarged (>1 cm) and tender anterior cervical lymph nodes, palatal petechiae, strawberry tongue, scarlatiniform rash
• viral: afebrile, absent/mild tonsillar exudates, minor and non-tender adenopathy, viral exanthems

Investigations
• no single sign or symptom reliably identifies GAS as the causative organism in children with sore throat
• scores are used to predict if throat culture will be positive (e.g. McIsaac Criteria)
  ▪ these score systems have not been found to be sensitive or specific enough to diagnose GAS in children and adolescents with sore throat
• suspected diagnosis of GAS pharyngitis should be confirmed with a rapid streptococcal antigen test and a follow-up throat culture if the rapid test is negative

Management
• antibiotics (for GAS/S. pyogenes)
  ▪ penicillin V or amoxicillin or erythromycin (if penicillin allergy) x 10 d
  ▪ can prevent rheumatic fever if given within 9 d of symptoms; does NOT alter risk of post-streptococcal GN
• supportive: hydration and acetaminophen for discomfort due to pain and/or fever
• follow-up: if uncomplicated course, no follow-up or post-antibiotic throat cultures needed
• prophylaxis: consider tonsillectomy for proven, recurrent streptococcal tonsillitis

Complications
• preventable with antibiotics: AOM, sinusitis, cervical adenitis, mastoiditis, retropharyngeal/peritonsillar abscess, sepsis
• immune-mediated complications: scarlet fever, acute rheumatic fever, post-streptococcal GN, reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A Streptococci (i.e. PANDAS)

SCARLET FEVER
• diffuse erythematous eruption
• delayed-type hypersensitivity reaction to pyrogenic exotoxin produced by GAS
• acute onset of fever, sore throat, strawberry tongue
• 24-48 h after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa; Pastia's lines may be accentuated in flexural areas
• within 24 h, sandpaper rash becomes generalized with perioral sparing, non-pruritic, non-painful, blanchable
• rash fades after 3-4 d, may be followed by desquamation
• treatment is penicillin, amoxicillin, or erythromycin x 10 d

RHEUMATIC FEVER
• inflammatory disease due to antibody cross-reactivity following GAS infection
• affects ~1:10,000 children in developed world; much more prevalent in developing nations; peak incidence at 5-15 yr of age
• mainly a clinical diagnosis based on Jones Criteria (revised):
  ▪ requires 2 major OR 1 major and 2 minor PLUS evidence of preceding strep infection (history of scarlet fever, GAS pharyngitis culture, positive rapid Ag detection test, ASOTs)
• treatment: penicillin or erythromycin for acute course x 10 d, prednisone if severe carditis
• secondary prophylaxis with daily penicillin or erythromycin
• complications
  ▪ acute: myocarditis, conduction system aberrations (sinus tachycardia, atrial fibrillation), valvulitis (acute MR), pericarditis
  ▪ chronic: valvular heart disease (mitral and/or aortic insufficiency/stenosis), infectious endocarditis ± thromboembolic phenomenon
  ▪ onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
POST-STREPTOCOCCAL GLOMERULONEPHRITIS
- most common in children aged 4-8 yr old; M>F
- antigen-antibody mediated complement activation with diffuse, proliferative GN
- occurs 1-3 wk following initial GAS infection (skin or throat)
- clinical presentation varies from asymptomatic, microscopic and macroscopic hematuria (colored urine) to all features of nephritic syndrome (see P81)
- diagnosis is confirmed with elevated serum antibody titers against streptococcal antigens (ASOT, anti-DNAse B), low serum complement (C3)
- management
  - symptomatic: fluid and sodium restrictions; loop diuretics for HTN and edema
  - in severe cases, may require dialysis if renal function significantly impaired
  - treat with penicillin or erythromycin if evidence of persistent GAS infection
- 95% of children recover completely within 1-2 wk; 5-10% have persistent hematuria

Meningitis

Definition
- inflammation of the meninges surrounding the brain and spinal cord

Epidemiology
- peak age: 6-12 mo; 90% of cases occur in children <5 yr old

Etiology
- viral: enteroviruses, HSV
- bacterial: age-related variation in specific pathogens
- fungal and parasitic meningitis also possible
- most often due to hematogenous spread or direct extension from a contiguous site

Risk Factors
- unvaccinated
- immunocompromised: asplenia, DM, HIV, prematurity
- recent or current infections: AOM, sinusitis, orbital cellulitis
- neuroanatomical: congenital defects, dermal sinus, neurosurgery, cochlear implants, recent head trauma
- exposures: day care centers, household contact, recent travel

History
- signs and symptoms variable and dependent on age, duration of illness, and host response to infection
- infants: fever, lethargy, irritability, poor feeding, N/V, diarrhea, respiratory distress, seizures
- children: fever, headache, photophobia, N/V, confusion, back/neck pain/stiffness, lethargy, irritability

Physical Exam
- infants: toxic, hypothermia, bulging anterior fontanelle, respiratory distress, apnea, petechial/purpuric rash, jaundice
- children: toxic, ↓ LOC, nuchal rigidity, Kernig's and Brudzinski's signs, focal neurologic findings, petechial/purpuric rash

Investigations
- blood work: CBC, electrolytes, Cr, BUN, glucose, C&S
- LP required for definitive diagnosis
  - Gram stain, bacterial C&S, WBC count and differential, RBC count, glucose, protein concentration
  - acid-fast stain if suspect TB
  - PCR for specific bacteria if available (helpful if already treated with antibiotics)
  - urinalysis and urine C&S in infants, Gram stain and culture of petechial/purpuric lesions
  - HSV and enterovirus PCR if suspected
Table 24. CSF Findings of Meningitis

<table>
<thead>
<tr>
<th>Component</th>
<th>Normal Child</th>
<th>Normal Newborn</th>
<th>Bacterial Meningitis</th>
<th>Viral Meningitis</th>
<th>Herpes Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (/µL)</td>
<td>0-6</td>
<td>0-30</td>
<td>&gt;1,000 (cloudy, xanthochromic)</td>
<td>100-500*</td>
<td>10-1,000</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>0</td>
<td>2-3</td>
<td>&gt;50</td>
<td>&lt;40</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>2.2-4.4</td>
<td>1.8-6.7</td>
<td>&gt;1.66</td>
<td>&gt;1.66</td>
<td>&gt;1.66</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>0.2-0.3</td>
<td>0.19-1.49</td>
<td>&gt;1.0</td>
<td>0.50-1.0</td>
<td>&gt;0.75</td>
</tr>
<tr>
<td>RBC (/µL)</td>
<td>0-2</td>
<td>0-2</td>
<td>0-10</td>
<td>0-2</td>
<td>10-50</td>
</tr>
</tbody>
</table>


Management

- supportive care
  - preservation of adequate cerebral perfusion by maintaining normal BP and managing ↑ ICP
  - close monitoring of fluids, electrolytes, glucose, acid-base disturbances, coagulopathies
- bacterial meningitis
  - if suspected or cannot be excluded, commence empiric antibiotic therapy while awaiting cultures or if LP contraindicated or delayed
  - adjuvant dexamethasone BEFORE antibiotic for Hib meningitis; consider for those >6 wk with pneumococcal meningitis
  - isolation with appropriate infection control procedures until 24 h after culture-sensitive antibiotic therapy
  - fluid restrict if any concern for SIADH
  - hearing test
  - report to Public Health; prophylactic antibiotics for close contacts of Hib and N. meningitidis meningitis

Table 25. Antibiotic Management of Bacterial Meningitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Main Pathogens</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-28 d</td>
<td>GBS, E. coli, Listeria Other: Gram-negative bacilli</td>
<td>Ampicillin + cefotaxime</td>
</tr>
<tr>
<td>28-90 d</td>
<td>Overlap of neonatal pathogens and those seen in older children</td>
<td>Ampicillin + cefotaxime ± vancomycin</td>
</tr>
<tr>
<td>&gt;90 d</td>
<td>S. pneumoniae, N. meningitidis</td>
<td>Ceftriaxone ± vancomycin</td>
</tr>
</tbody>
</table>

- viral meningitis
  - mainly supportive (except for HSV)
  - acyclovir for HSV meningitis
  - report to Public Health
  - prophylaxis: appropriate vaccinations significantly decrease incidence of bacterial meningitis (see Routine Immunization, P3)

Complications

- mortality: neonate 15-20%, children 4-8%; pneumococcus > meningococcus > Hib
- acute: SIADH, subdural effusion/empyema, brain abscess, disseminated infection (osteomyelitis, septic arthritis, abscess), shock/DIC
- chronic: hearing loss, neuromotor/cognitive delay, learning disabilities, neurological deficit, seizure disorder, hydrocephalus

Mumps

Definition

- acute, self-limited viral infection that is most commonly characterized by adenitis and swelling of the parotid glands

Epidemiology

- incidence has declined since introduction of two-dose MMR vaccination schedule
- average of 25 reported cases per yr
- majority of reported cases in children between 5-10 yr of age

Etiology

- mumps virus (RNA virus of the genus Rubulavirus in the Paramyxoviridae family)
- transmission via respiratory droplets, direct contact, fomites
- incubation period: 14-25 d
• infectivity period: 7 d pre-parotitis to 5 d post-parotitis
• upper respiratory tract → lymph nodes → salivary glands, gonads, pancreas, meninges, kidney, heart, thyroid

**History**
• non-specific prodome of fever, headache, malaise, myalgias (especially neck pain)
• usually followed within 48 h by parotid swelling secondary to parotitis (bilateral, preauricular, ear pushed up and out)
• parotid gland is tender and pain worsened with spicy or sour foods
• one third of infections do not cause clinically apparent salivary gland swelling and may simply present as an URTI

**Investigations**
• clinical diagnosis, but may be confirmed with IgM positive serology within 4 wk of acute infection
  ▪ may also use PCR or viral cultures from oral secretions, urine, blood, and CSF
  ▪ blood work: CBC (leukopenia with relative lymphocytosis), serum amylase (elevated)

**Management**
• mainly supportive: analgesics, antipyretics, warm or cold packs to parotid may be soothing
• admit to hospital if serious complications (meningitis, pancreatitis)
• droplet precautions recommended until 5 d after onset of parotid swelling
• prophylaxis: routine vaccination (see **Routine Immunization**, P3)

**Complications**
• common: aseptic meningitis, orchitis/oophoritis
• less common: encephalitis, pancreatitis, thyroiditis, myocarditis, arthritis, GN, ocular complications, hearing impairment

---

**Pertussis**

**Definition**
• prolonged respiratory illness characterized by paroxysmal coughing and inspiratory “whoop”

**Epidemiology**
• ~10 million children <1 yr old affected worldwide, causes up to 400,000 deaths per yr
• greatest incidence among children <1 yr (not fully immunized) and adolescents (waning immunity)

**Etiology**
• *Bordetella pertussis*: Gram negative pleomorphic rod
• highly contagious; transmitted via respiratory droplets released during intense coughing
• incubation period: 6-20 d; most contagious during catarrhal phase but may remain contagious for weeks after

**History**
• prodromal catarrhal stage
  ▪ lasts 1-7 d; URTI symptoms (coryza, mild cough, sneezing) with NO or LOW-GRADE fever
• paroxysmal stage
  ▪ lasts 4-6 wk; characterized by paroxysms of cough (“100 day cough”), sometimes followed by inspiratory whoop (“whooping cough”)
  ▪ infants <6 mo may present with post-tussive apnea, whoop is often absent
  ▪ onset of attacks precipitated by yawning, sneezing, eating, physical exertion
  ▪ ± post-tussive emesis, may become cyanotic before whoop
• convalescent stage
  ▪ lasts 1-2 wk; characterized by occasional paroxysms of cough, but decreased frequency and severity
  ▪ non-infectious but cough may last up to 6 mo

**Investigations**
• NP specimen using aspirate or NP swab
  ▪ gold standard: culture using special media (Regan-Lowe agar)
  ▪ PCR to detect pertussis antigens
• blood work: CBC (lymphocytosis) and serology (antibodies against *B. pertussis*)

**Management**
• admit if paroxysms of cough are associated with cyanosis and/or apnea and give O₂
• supportive care
• antimicrobial therapy indicated if *B. pertussi* isolated, or symptoms present for <21 d
  ▪ use macrolide antibiotics (azithromycin, erythromycin, or clarithromycin)
• droplet isolation until 5 d of treatment and report to Public Health
• prophylaxis
  ▪ macrolide antibiotics for all household contacts
  ▪ prevention with vaccination in infants and children (Pentacel®), and booster in adolescents
    (Adacel®) (see *Routine Immunization*, P3)

Complications
• pressure-related from paroxysms: subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
• respiratory: sinusitis, pneumonia, aspiration, atelectasis, pneumomediastinum, pneumothorax, alveolar rupture
• neurological: seizures (~3%), encephalopathy, ICH
• mortality: ~0.3%; highest risk in infants <6 mo old

### Pneumonia
• see *Pediatric Respiratory*, P90

### Periorbital (Preseptal) and Orbital Cellulitis
• see *Ophthalmology*, OP10

### Sexually Transmitted Disease
• see *Family Medicine*, FM45 and *Gynecology*, GY25

### Sinusitis
• see *Family Medicine*, FM46
• complication of ≤10% of URTIs in children
• clinical diagnosis
• diagnostic imaging is NOT required to confirm diagnosis in children
  ▪ routine CT not recommended, but consider if suspect complications of sinusitis, persistent/recurrent disease, need for surgery
• antibiotic therapy for all children (although nearly half resolve spontaneously within 4 wk)
• complications: preseptal/orbital (preseptal/orbital cellulitis, orbital abscess, osteomyelitis, etc.), intracranial (meningitis, abscess, etc.), Pott’s Puffy tumor

### Urinary Tract Infection

#### Definition
• infection of the urinary bladder (cystitis) and/or kidneys (pyelonephritis)

#### Epidemiology
• overall prevalence in infants and young children presenting with fever is 7%
• <4-6 wk old: more common in boys
• >1 yr old: females have two- to four-fold higher prevalence

#### Etiology
• majority (>95%) have a monomicrobial cause (~70% *E. coli*)
• Gram-negative bacilli: *E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, *Pseudomonas*
• Gram-positive cocci: *S. saprophyticus*, *Enterococcus*

#### Risk Factors
• non-modifiable: female gender, Caucasian, previous UTIs, family history
• modifiable: urinary tract abnormalities (VUR, neurogenic bladder, obstructive uropathy, posterior urethral valve), dysfunctional voiding, repeated bladder catheterization, uncircumcised males, labial adhesions, sexually active, constipation, toilet training
History
• infants and young child: often just fever or non-specific symptoms (poor feeding, irritability, FTT, jaundice if <28 d old, vomiting)
• older child: fever, urinary symptoms (dysuria, urgency, frequency, incontinence, hematuria), abdominal and/or flank pain

Physical Exam
• infants and young child: toxic vs. non-toxic, febrile, FTT, jaundice; look for external genitalia abnormalities (phimosis, labial adhesions) and lower back signs of occult myelodysplasia (e.g. hair tufts), which may be associated with neurogenic bladder
• older child: febrile, suprapubic and/or CVA tenderness, abdominal mass (enlarged bladder or kidney); may present with short stature, FTT or HTN secondary to renal scarring from previously unrecognized or recurrent UTIs

Investigations
• sterile urine specimen
  ▪ clean catch, catheterization, or suprapubic aspiration
  ▪ urinalysis (leukocyte esterase, nitrites, erythrocytes, hemoglobin), microscopy (bacteria and leukocytes, erythrocytes), C&S
• diagnosis established if urinalysis suggests infection AND if ≥50,000 colony-forming units per mL of a uropathogen cultured

Management
• admit if: <2 mo old, urosepsis, persistent vomiting, inability to tolerate oral medication, moderate-severe dehydration, immunocompromised, complex urologic pathology, inadequate follow-up, failure to respond to outpatient therapy
• supportive care: maintenance of hydration and adequate pain control
• antibiotics
  ▪ base on local antimicrobial susceptibility patterns
  ▪ commence broad empiric therapy until results of urine C&S known, and then tailor as appropriate
  ▪ neonates: IV ampicillin and gentamicin
  ▪ infants and older children: oral cephalexin if outpatient; IV ampicillin and gentamicin if inpatient
  ▪ duration 7-14 d
• imaging
  ▪ renal and bladder U/S for all febrile infants with UTIs looking for anatomical abnormalities, hydronephrosis, abscess
  ▪ VCUG not recommended after 1st febrile UTI unless U/S reveals hydronephrosis, obstructive uropathies or other signs suggestive of high-grade VUR
• follow-up: outpatients to return in 24-48 h if no clinical response and seek prompt medical evaluation for future febrile illnesses
• prophylaxis: generally not recommended unless higher grades of VUR

Complications
• long-term morbidity: focal renal scarring develops in 8% of patients; long-term significance unknown

Neonatology

Gestational Age and Size

Definitions
• classification by GA
  ▪ preterm: <37 wk
  ▪ near-term: 35-37 wk
  ▪ term: 37-42 wk
  ▪ post-term: >42 wk
• classification by birth weight
  ▪ SGA: 2 SD < mean weight for GA or <10th percentile
  ▪ AGA: within 2 SD of mean weight for GA
  ▪ LGA: 2 SD > mean weight for GA or >90th percentile

Sensitivity and Specificity of Urine Dip in Children

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microscopy leukocytes</td>
<td>73%</td>
<td>81%</td>
</tr>
<tr>
<td>Nitrites</td>
<td>53%</td>
<td>98%</td>
</tr>
<tr>
<td>Leukocyte esterase</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>Microscopy bacteriuria</td>
<td>81%</td>
<td>83%</td>
</tr>
<tr>
<td>Leukocyte esterase or</td>
<td>99.8%</td>
<td>70%</td>
</tr>
<tr>
<td>nitrites, or microscopy positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pediatrics 2011;128:595-610

Prophylaxis After First Febrile Urinary Tract Infection in Children? A Multicenter, Randomized Controlled, Noninferiority Trial

Pediatrics 2008;122:1064-1071

Study: Randomized, controlled, open-label, 2 armed, noninferiority trial.
Patients: 338 patients aged 2 mo-<7 yr who had a first episode of febrile UTI.
Intervention: No prophylaxis vs. prophylaxis.
Outcome: Recurrence rate of febrile UTI and rate of renal scarring.
Results: No significant difference in recurrence rate or in the rate of renal scarring between the prophylaxis and no prophylaxis group.

Dubowitz/Ballard Scores

GA can be determined after birth using Dubowitz/Ballard scores:
• Assessment at delivery of physical maturity (e.g. plantar creases, lanugo, ear maturation) and neuromuscular maturity (e.g. posture, arm recoil) translates into a score from -10 to +50
• Higher score means greater maturity (increased GA)
  • -10 = 20 wk, +50 = 44 wk
  • Ideal = 35-40, which corresponds to GA 38-40 wk
• Only accurate ± 2 wk
Table 26. Abnormalities of Gestational Age and Size

<table>
<thead>
<tr>
<th>Features</th>
<th>Causes</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Term Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;37 wk</td>
<td>Spontaneous: cause unknown</td>
<td>RDS, apnea of prematurity, chronic lung disease, bronchopulmonary dysplasia</td>
</tr>
<tr>
<td></td>
<td>Maternal disease: HTN, DM, cardiac and renal disorders</td>
<td>Feeding difficulties, NEC</td>
</tr>
<tr>
<td></td>
<td>Fetal conditions: multiple pregnancy, congenital abnormalities</td>
<td>Hypocalcemia, hypoglycemia, hypothermia</td>
</tr>
<tr>
<td></td>
<td>Pregnancy issues: placenta insufficiency, placenta previa, uterine malformations, previous preterm birth, infection</td>
<td>Anemia, jaundice</td>
</tr>
<tr>
<td></td>
<td>Behavioral and psychological contributors: smoking, EtOH, drug use, psychosocial stressors</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td></td>
<td>Sociodemographic factors: age, socioeconomic conditions</td>
<td>ICH/IVH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PDA</td>
</tr>
<tr>
<td>Post-Term Infants</td>
<td>Most cases unknown</td>
<td>Increased risk of stillbirth or neonatal death</td>
</tr>
<tr>
<td>&gt;42 wk</td>
<td>Increased in first pregnancies</td>
<td>Increased birthweight</td>
</tr>
<tr>
<td></td>
<td>Previous post-term birth</td>
<td>Fetal “postmaturity syndrome”: impaired growth due to placental dysfunction</td>
</tr>
<tr>
<td></td>
<td>Genetic factors</td>
<td>Meconium aspiration</td>
</tr>
<tr>
<td>SGA Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td>Extrinsin causes: placenta insufficiency, poor nutrition, HTN, multiple pregnancies, drugs, EtOH, smoking</td>
<td>Perinatal hypoxia</td>
</tr>
<tr>
<td>Asymmetric (head-sparing): late onset, growth arrest</td>
<td></td>
<td>Hypoglycemia, hypocalcemia, hypothermia</td>
</tr>
<tr>
<td>Symmetirc: early onset, lower growth</td>
<td>Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic</td>
<td>Hyperviscosity (polycythemia), jaundice, hypomotility</td>
</tr>
<tr>
<td>LGA Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;90th percentile</td>
<td>Maternal DM</td>
<td>Birth trauma, perinatal depression (meconium aspiration)</td>
</tr>
<tr>
<td></td>
<td>Racial or familial factors</td>
<td>RDS, TTN</td>
</tr>
<tr>
<td></td>
<td>Increasing parity</td>
<td>Jaundice, polycythemia</td>
</tr>
<tr>
<td></td>
<td>Previous LGA infant, high BMI, large pregnancy weight gain</td>
<td>Hypoglycemia, hypocalcemia</td>
</tr>
</tbody>
</table>

Routine Neonatal Care

1. Erythromycin ointment: applied to both eyes for prophylaxis of ophthalmia neonatorum
2. Vitamin K IM: prophylaxis against HDNB
3. Newborn screening tests
   - Metabolic disorders (amino acid disorders, organic acid disorders, fatty acid oxidation defects, biotinidase deficiency, galactosemia)
   - Blood disorders (SCD, other hemoglobinopathies)
   - Endocrine disorders (CAH, congenital hypothyroidism)
   - Others (CF, SCID)
   - Congenital hearing loss
4. If mother Rh negative: send cord blood for blood group and direct antiglobulin test
5. If mother hepatitis B surface antigen positive: HB Ig and start hepatitis B vaccine series

Neonatal Resuscitation

- Assess Apgar score at 1 and 5 min
- If <7 at 5 min then reassess q5min, until >7
- Do not wait to assign Apgar score before initiating resuscitation

Table 27. Apgar Score

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>Absent</td>
<td>&lt;100/min</td>
<td>&gt;100/min</td>
</tr>
<tr>
<td>Respiratory Effort</td>
<td>Absent</td>
<td>Slow, irregular</td>
<td>Good, crying</td>
</tr>
<tr>
<td>Irritability</td>
<td>No response</td>
<td>Grimace</td>
<td>Cough/cry</td>
</tr>
<tr>
<td>Tone</td>
<td>Limp</td>
<td>Some flexion of extremities</td>
<td>Active motion</td>
</tr>
<tr>
<td>Color</td>
<td>Blue, pale</td>
<td>Body pink, extremities blue (acrocyanosis)</td>
<td>Completely pink</td>
</tr>
</tbody>
</table>
Initial Resuscitation

- anticipation: know maternal history, history of pregnancy, labor, and delivery
- steps to take for all infants (before ABCs)
  - warm (radiant heater, warm towels) and dry the newborn (remove wet towels)
  - position and clear airway (“sniffing” position)
  - stimulate infant: rub lower back gently or flick soles of feet EXCEPT if meconium present (in which case tracheal suction first)
  - assess breathing and heart rate
- Airway
  - if meconium is present and
    - baby is vigorous (strong respiratory effort, good muscle tone, HR >100): no further resuscitative interventions required
    - baby is not vigorous: intubate and suction trachea while monitoring vital signs; if prolonged or unsuccessful intubation, attempt bag mask ventilation
  - if no meconium and suction required, suction mouth first and then nose
- Breathing
  - if HR <100 or apneic, apply PPV
  - PPV at rate of 40-60/min with enough pressure to see visible chest expansion and note increase in HR
  - monitor preductal SpO₂
  - if PPV not effective (no increase in HR, no chest rise, low SpO₂), incorporate corrective actions
- Circulation
  - if HR <60 after 30 s of effective ventilation, start chest compressions ("60 or less, compress")
  - should provide 100% oxygen as soon as chest compressions are required
  - chest compressions at lower 1/3 of the sternum and 1/3 of the AP depth at a rate of 120 events per min (3 compressions:1 ventilation = 120 compressions/min:40 breaths/min)

### Table 28. Interventions Used in Neonatal Resuscitation

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>0.1-0.3 mL/kg/dose of 1:10,000 (0.01-0.03 mg/kg) IV 0.5-1 mL/kg/dose of 1:10,000 (0.05-0.1 mg/kg) endotracheally can be considered while awaiting IV access (IV preferred)</td>
<td>HR &lt;60 and not rising</td>
<td>Side effects: tachycardia, HTN, cardiac arrhythmias</td>
</tr>
<tr>
<td>Naloxone (Narcan®)</td>
<td>0.1 mg/kg IV/IM</td>
<td>Not recommended as part of initial resuscitation HR and oxygenation should be restored by supporting ventilation</td>
<td>Do not use for chronic opiate exposure – may cause withdrawal symptoms including HTN, irritability, seizures Action of opioid outlasts action of naloxone therefore close monitoring required after administration</td>
</tr>
<tr>
<td>Fluid Bolus (NS, whole blood, Ringer’s lactate)</td>
<td>10 mL/kg</td>
<td>Evidence of hypovolemia</td>
<td>May need to be repeated Avoid giving too rapidly as large volume rapid infusions can be associated with IVH</td>
</tr>
</tbody>
</table>

**Approach to the Depressed Newborn**

- a depressed newborn lacks one or more of the following characteristics of a normal newborn
  - pulse >100 bpm
  - cries when stimulated
  - actively moves all extremities
  - has a good strong cry
- approximately 10% of newborn babies require assistance with breathing after delivery

**Targeted Preductal SpO₂ After Birth**

- 1 min 60-65%
- 2 min 65-70%
- 3 min 70-75%
- 4 min 75-80%
- 5 min 80-85%
- 10 min 85-95%

**Corrective Actions for PPV in Neonatal Resuscitation**

- MR SOPA
  - Mask readjustment
  - Reposition airway
  - Suction mouth and nose
  - Open mouth
  - Pressure increase
  - Alternative airway
Table 29. Etiology of Respiratory Depression in the Newborn

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Problems</td>
<td>RDS/hyaline membrane disease</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypoplasia</td>
</tr>
<tr>
<td></td>
<td>CNS depression</td>
</tr>
<tr>
<td></td>
<td>MAS</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
</tr>
<tr>
<td></td>
<td>Pleural effusions</td>
</tr>
<tr>
<td></td>
<td>Congenital malformations</td>
</tr>
<tr>
<td>Anemia (severe)</td>
<td>Erythroblastosis fetalis</td>
</tr>
<tr>
<td></td>
<td>Secondary hydrops fetalis</td>
</tr>
<tr>
<td>Maternal Causes</td>
<td>Drugs/anesthesia (opiates, magnesium sulphate)</td>
</tr>
<tr>
<td></td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Maternal myasthenia gravis</td>
</tr>
<tr>
<td>Congenital Malformations/Birth Injury</td>
<td>Nuchal cord, perinatal depression</td>
</tr>
<tr>
<td></td>
<td>Bilateral phrenic nerve injury</td>
</tr>
<tr>
<td></td>
<td>Potter’s sequence</td>
</tr>
<tr>
<td>Shock</td>
<td>Antepartum hemorrhage</td>
</tr>
<tr>
<td>CHD</td>
<td>Transposition of the great arteries with intact ventricular septum</td>
</tr>
<tr>
<td>Other</td>
<td>Hypothermia</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Infection</td>
</tr>
</tbody>
</table>

**Diagnosis**
- vital signs
- detailed maternal history: include prenatal care, illnesses, use of drugs, labor, previous high risk pregnancies, infections during pregnancy, current infections, duration of ruptured membranes, blood type and Rh status, amniotic fluid status, GA, meconium, Apgar scores
- clinical findings (observe for signs of respiratory distress such as cyanosis, tachypnea, retractions, grunting, temperature instability)
- laboratory results (CBC, ABG, blood type, glucose)
- transillumination of chest to evaluate for pneumothorax
- CXR

**Management**
- ABCs
- intubation and suction if meconium present
- apply tactile stimulation if no meconium
- provide PPV if apneic OR HR <100 bpm
- monitor SpO₂ and HR (if <60 bpm, start chest compressions)
- provide ventilatory support and treat the underlying cause

**Common Conditions of Neonates**

**Apnea**

**Definition**
- “periodic breathing”: normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with pauses lasting 5-10 s
- “apnea”: absence of respiratory gas flow for >20 s (or less if associated with bradycardia or desaturation) – 3 types
  - central: no chest wall movement, no signs of obstruction
  - obstructive: chest wall movement continues against obstructed upper airway, no airflow
  - mixed: combination of central and obstructive apnea

**Differential Diagnosis**
- in term infants, apnea requires full workup as it can be associated with sepsis
- other causes
  - CNS
    - apnea of prematurity (<34 wk): combination of CNS immaturity and obstructive apnea; resolves by 36 wk GA; diagnosis of exclusion
    - seizures
    - ICH
    - hypoxic injury
- infectious: sepsis, meningitis, NEC
- GI: GERD, aspiration with feeding
- metabolic: hypoglycemia, hyponatremia, hypocalcemia, inborn error of metabolism
- cardiovascular: anemia, hypovolemia, PDA, heart failure
- medications: morphine

Management
- O₂, ventilatory support, maintain normal blood gases
- tactile stimulation
- correct underlying cause
- medications: methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)

## Bleeding Disorders in Neonates

### Clinical Presentation
- oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), subgaleal hemorrhage and prolonged bleeding following circumcision

### Etiology
- 4 major categories
  - increased platelet destruction: maternal ITP or SLE, infection/sepsis, DIC, neonatal alloimmune thrombocytopenia, autoimmune thrombocytopenia
  - decreased platelet production/function: pancytopenia, bone marrow replacement, Fanconi anemia, Trisomy 13 and 18
  - metabolic: congenital thyrotoxicosis, inborn error of metabolism
  - coagulation factor deficiencies (see Hematology, H29): hemophilia A/B, HDNB

### NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

#### Epidemiology
- 1 per 4,000-5,000 live births

#### Pathophysiology
- platelet equivalent of Rh disease of the newborn
- occurs when mother is negative for HPA and fetus is positive
- development of maternal IgG antibodies against HPA antigens on fetal platelets

#### Clinical Presentation
- petechiae, purpura, thrombocytopenia in otherwise healthy neonate
- severe disease can lead to intracranial bleeding

#### Diagnosis
- maternal and paternal platelet typing and identification of platelet alloantibodies

#### Treatment
- IVIg to mother prenatally starts in second trimester ± steroids ± fetal platelet transfusions
- treat neonate with IVIg
- if transfusion required should be with washed maternal platelets or donor HPA negative platelets

### AUTOIMMUNE THROMBOCYTOPENIA

#### Pathophysiology
- caused by antiplatelet antibodies from maternal ITP or SLE
- passive transfer of antibodies across placenta

#### Clinical Presentation
- similar presentation to neonatal alloimmune thrombocytopenia, but thrombocytopenia usually less severe

#### Treatment
- steroids to mother for 10-14 d prior to delivery or IVIg to mother before delivery
- treat neonate with IVIg (usually if platelets <60,000)
- transfusion of infant with maternal/donor platelets only in severe cases, as antibodies will destroy transfused platelets
HEMORRHAGIC DISEASE OF THE NEWBORN

Pathophysiology
- caused by vitamin K deficiency
- factors II, VII, IX, X are vitamin K-dependent, therefore both PT and PTT are abnormal

Etiology and Clinical Presentation
- neonates at risk of vitamin K deficiency if: vitamin K poorly transferred across the placenta; maternal use of antiepileptics; insufficient bacterial colonization of colon at birth to synthesize vitamin K; breastfed (vitamin K intake inadequate in breastfed infants)
- neonate may present with hematomas, ICH (causing apnea or seizures), internal bleeding, hematuria, bruising, prolonged bleeding (often from mucous membranes, umbilicus, circumcision, and venipunctures)

Prevention
- vitamin K IM administration at birth to all newborns

Bronchopulmonary Dysplasia

Definition
- also known as chronic lung disease
- clinically defined as O₂ requirement for >28 d plus persistent need for oxygen and/or ventilatory support at 36 wk corrected GA
- damage to developing lungs with prolonged intubation/ventilation

Investigations
- CXR findings may demonstrate decreased lung volumes, areas of atelectasis, and hyperinflation

Treatment
- no good treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, but use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcomes

Prognosis
- chronic respiratory failure may lead to pulmonary HTN, poor growth, and right-sided heart failure
- patients with bronchopulmonary dysplasia may continue to have significant impairment and deterioration in lung function late into adolescence
- some lung abnormalities may persist into adulthood including airway obstruction, airway hyper-reactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcomes

Cyanosis

![Figure 12. Approach to neonatal cyanosis](image-url)
Management
• ABGs
  ▪ elevated CO₂ suggests respiratory cause
  ▪ hyperoxia test (to distinguish between cardiac and respiratory causes of cyanosis): get baseline PaO₂ in room air, then PaO₂ on 100% O₂ for 10-15 min
    • PaO₂ <150 mmHg: suggests cyanotic CHD or possible PPHN (see Pediatric Cardiology, P16)
    • PaO₂ >150 mmHg: suggests cyanosis likely due to respiratory or non-cardiac cause
• CXR: look for respiratory abnormalities (respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)

Diaphragmatic Hernia
• see General Surgery, GS12

Definition
• developmental defect of the diaphragm with herniation of abdominal organs into thorax
• associated with pulmonary hypoplasia and PPHN

Clinical Presentation
• respiratory distress, cyanosis
• scaphoid abdomen and barrel-shaped chest
• affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
• heart sounds shifted to contralateral side
• asymmetric chest movements, trachea deviated away from affected side
• may present outside of neonatal period
• often associated with other anomalies (cardiovascular, CNS, chromosomal abnormalities)
• CXR: bowel loops in thorax (usually left side), displaced mediastinum

Treatment
• immediate intubation required at birth: DO NOT bag mask ventilate because air will enter stomach and further compress lungs
• place large bore orogastric tube to decompress bowel
• initial stabilization and management of pulmonary hypoplasia and PPHN, hemodynamic support and surgery when stable

Hypoglycemia

Definition
• glucose <40 mg/dL

Etiology
• decreased carbohydrate stores: premature, SGA, RDS, maternal HTN
• endocrine: hormonal deficiencies (GH, cortisol, epinephrine), insulin excess (infant of diabetic mother, Beckwith-Wiedemann syndrome/islet cell hyperplasia), HPA axis suppression (panhypopituitarism)
• inborn errors of metabolism: fatty acid oxidation defects, galactosemia
• miscellaneous: sepsis, hypothermia, polycythemia

Clinical Findings
• signs often non-specific and subtle: lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

Management
• identify and monitor infants at risk (pre-feed blood glucose checks)
• begin oral feeds as soon as possible after birth and ensure regular feeds
• if significant and/or symptomatic hypoglycemia, provide glucose IV and titrate according to blood sugar levels
• if persistent hypoglycemia or no predisposing cause, send “critical blood work” during an episode of hypoglycemia: ABG, ammonia, β-hydroxybutyrate, cortisol, free fatty acids, GH, insulin, lactate, urine dipstick for ketones
Intraventricular Hemorrhage

Definition
• hemorrhage originating in the periventricular subependymal germinal matrix

Epidemiology
• incidence and severity inversely proportional to GA
• 50% of IVH occurs within 8 h of birth; 90% occurs by day 3

Risk Factors
• prematurity (<32 wk), BW <1,500 g, need for vigorous resuscitation at birth, pneumothorax, ventilated preterm infants, hemodynamic instability, RDS, coagulopathy

Clinical Presentation
• many infants with IVH are asymptomatic
• subtle signs: apnea, bradycardia, changes in tone or activity, altered LOC
• catastrophic presentation: bulging fontanelle, sudden drop in hematocrit, acidosis, seizures, hypotension

Classification
• Papile classification
• parenchymal hemorrhage may also occur in the absence of IVH
• routine head U/S screening of all preterm infants <32 wk or <1,500 g gestation throughout NICU stay
• consider MRI at term for extremely LBW infants

Management of Acute Hemorrhage
• supportive care to maintain blood volume and acid-base status
• avoid fluctuations in blood pressure and cerebral blood flow
• follow-up with serial imaging

Prognosis
• outcome depends on grade of IVH
• short-term sequelae for severe IVH: mortality, extension of bleed, posthemorrhagic hydrocephalus, posthemorrhagic infarction, cyst formation
• possible long-term major neurological sequelae: CP, cognitive deficits, motor deficits, visual and hearing impairment
• Grades I and II hemorraghes have a relatively favorable prognosis
• greatest morbidity and mortality is seen with Grade IV hemorrhage and posthemorrhagic hydrocephalus requiring ventriculoperitoneal shunt placement

Jaundice

Clinical Presentation
• jaundice is visible at serum bilirubin levels of 5 mg/dL; visual assessment is often misleading
• look at sclera, tip of nose in natural light
• jaundice more severe/prolonged (due to increased retention of bilirubin in the circulation) with: prematurity, acidosis, hypoalbuminemia, dehydration, hemolysis

Figure 13. Approach to neonatal hyperbilirubinemia
PHYSIOLOGIC JAUNDICE

Epidemiology
- term infants: onset 3-4 d of life, resolution by 10 d of life
- premature infants: higher peak and longer duration

Pathophysiology
- increased hematocrit and decreased RBC lifespan
- immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
- increased enterohepatic circulation

Breastfeeding Jaundice
- common; due to a lack of milk production → dehydration → exaggerated physiologic jaundice

Breast Milk Jaundice
- 1 per 200 breastfed infants
- glucuronyl transferase inhibitor found in breast milk
- onset 7 d of life, peak at 2-3 wk of life, usually resolved by 6 wk

<table>
<thead>
<tr>
<th>Table 30. Risk Factors for Jaundice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Factors</td>
</tr>
<tr>
<td>Ethnic group (e.g. Asian, native American)</td>
</tr>
<tr>
<td>Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility)</td>
</tr>
<tr>
<td>Breastfeeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 31. Causes of Neonatal Jaundice by Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 h</td>
</tr>
<tr>
<td>ALWAYS PATHOLOGIC</td>
</tr>
<tr>
<td>Hemolytic</td>
</tr>
<tr>
<td>Rh or ABO incompatibility</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Congenital infection (TORCH)</td>
</tr>
<tr>
<td>Severe bruising/hemorrhage</td>
</tr>
<tr>
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</tbody>
</table>

PATHOLOGIC JAUNDICE
- all cases of conjugated hyperbilirubinemia; some cases of unconjugated hyperbilirubinemia are pathologic

Investigations
- unconjugated hyperbilirubinemia
  - hemolytic workup: CBC, reticulocyte count, blood group (mother and infant), peripheral blood smear, Coombs test
  - if baby is unwell or has fever: septic workup (CBC and differential, blood and urine cultures ± LP, CXR)
  - other: G6PD screen (especially in males), TSH
- conjugated hyperbilirubinemia must be investigated without delay
  - consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic workup, galactosemia screen (erythrocyte galactose-1-phosphate uridyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat chloride

TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA
- to prevent kernicterus
- breastfeeding does not usually need to be discontinued, ensure adequate feeds and hydration
- lactation consultant support, mother to pump after feeds
- treat underlying causes (e.g. sepsis)
- phototherapy (blue-green wavelength, not UV light)
  - insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
  - serum bilirubin should be monitored during and immediately after therapy (risk of rebound because photoisomerization reversible when phototherapy discontinued)
- contraindicated in conjugated hyperbilirubinemia: results in “bronzed” baby
- side effects: skin rash, diarrhea, eye damage (eye shield used routinely for prevention), dehydration
- use published guidelines and nomogram for initiation of phototherapy
- exchange transfusion
  - indications: high bilirubin levels as per published graphs based on age, weeks gestation
  - use of IV Ig in case of severe hyperbilirubinemia (DAT+) becoming evidence-based practice

KERNICTERUS

Etiology
- unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin is deposited in the brain resulting in permanent damage (typically basal ganglia or brainstem)
- incidence increases as serum bilirubin levels increase above 19.8 mg/dL.
- can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, acidosis, hypothermia, hypoglycemia, and prematurity

Clinical Presentation
- up to 15% of infants have no obvious neurologic symptoms
- early stage: lethargy, hypotonia, poor feeding, emesis (bilirubin encephalopathy)
- mid stage: hypertonia, high pitched cry, opisthotonic posturing (back arching), bulging fontanelle, seizures, pulmonary hemorrhage
- late stage (first year and beyond)
  - hypotonia, delayed motor skills, extrapyramidal abnormalities (choreoathetoid CP), gaze palsy, mitral regurgitation, sensorineural hearing loss

Prevention
- exchange transfusion, IV Ig if indicated

BILIARY ATRESIA

Definition
- atresia of the extrahepatic bile ducts which leads to cholestasis and increased conjugated bilirubin after the first week of life
- progressive obliterative cholangiopathy

Epidemiology
- incidence: 1:10,000-15,000 live births
- associated anomalies in 10-35% of cases: situs inversus, congenital heart defects, polysplenia

Clinical Presentation
- dark urine, pale stool, jaundice (persisting for >2 wk), abdominal distension, hepatomegaly

Diagnosis
- conjugated hyperbilirubinemia, abdominal U/S
- HIDA scan (may be bypassed in favor of biopsy if timing of diagnosis is critical)
- liver biopsy

Treatment
- surgical drainage procedure
- hepatopancreaticoenterostomy (Kasai procedure; most successful if <8 wk of age)
- two-thirds will eventually require liver transplantation
- vitamins A, D, E, and K; diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

Necrotizing Enterocolitis

Definition
- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon

Epidemiology
- affects 1-5% of preterm newborns admitted to NICU
Pathophysiology
- postulated mechanism of bowel ischemia: mucosal damage and enteral feeding → bacterial growth → bowel necrosis/gangrene/perforation

Risk Factors
- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis

Clinical Presentation
- usually presents at 2-3 wk of age
- distended abdomen
- increased amount of gastric aspirate/vomitus with bile staining
- frank or occult blood in stool
- feeding intolerance
- diminished bowel sounds
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

Investigations
- AXR: pneumonitis intestinalis (intramural air is a hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, lactate, blood culture, electrolytes
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnea

Treatment
- NPO (7-10 d), vigorous IV fluid resuscitation, decompression with NG tube, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 d)
- serial AXRs detect early perforation (40% mortality in perforated NEC)
- peritoneal drain/surgery if perforation

Persistent Pulmonary Hypertension of the Newborn

Epidemiology
- incidence 1.9 per 1,000 live births

Clinical Presentation
- usually presents within 12 h of birth with severe hypoxemia/cyanosis; may have only mild respiratory distress

Pathophysiology
- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- R → L shunt through PDA, foramen ovale → decreased pulmonary blood flow and hypoxemia → further pulmonary vasoconstriction

Risk Factors
- secondary PPHN: asphyxia, MAS, RDS, sepsis, pneumonia, structural abnormalities (e.g. diaphragmatic hernia, pulmonary hypoplasia)
- primary PPHN occurs in absence of risk factors
- more common in term or post-term infants

Investigations
- measure pre- and post-ductal oxygen levels
- hyperoxia test to exclude CHD
- ECG (RV strain)
- Echo reveals increased pulmonary arterial pressure and a R → L shunt across PDA and patent foramen ovale; also used to rule out other cardiac defects

Treatment
- maintain good oxygenation (SaO2 >95%) in at-risk infants
- O2 given early and tapered slowly, minimize stress and metabolic demands, maintain normal blood gases, circulatory support
- mechanical ventilation, high frequency oscillation in a sedated muscle-relaxed infant
- nitric oxide, surfactant
- extracorporeal membrane oxygenation used in some centers when other therapy fails
Respiratory Distress in the Newborn

Clinical Presentation
- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, subcostal/intercostal indrawing, nasal flaring
- dusky, central cyanosis
- decreased air entry, crackles on auscultation

Differential Diagnosis of Respiratory Distress
- pulmonary: RDS, TTN, MAS, pleural effusion, pneumothorax, congenital lung malformations
- infectious: sepsis, pneumonia
- cardiac: CHD (cyanotic, acyanotic), PPHN
- hematologic: blood loss, polycythemia
- anatomic: TEF, congenital diaphragmatic hernia, mucus or meconium plug, upper airway obstruction (see Otolaryngology, OT44)
- metabolic: hypoglycemia, inborn errors of metabolism
- neurologic: CNS damage (trauma, hemorrhage), drug withdrawal syndromes

Investigations
- CXR, ABG (or venous blood gas from umbilical venous line)
- CBC, blood cultures, blood glucose
- Echo, ECG if indicated

<table>
<thead>
<tr>
<th>Table 32. Distinguishing Features of RDS, TTN, MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Distress Syndrome (RDS)</strong></td>
</tr>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>Gestational Age</td>
</tr>
<tr>
<td>Risk Factors</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Clinical Presentation</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>CXR Findings</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>Prevention</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Treatment</td>
</tr>
</tbody>
</table>
Table 32. Distinguishing Features of RDS, TTN, MAS (continued)

<table>
<thead>
<tr>
<th>Complications</th>
<th>RDS</th>
<th>TTN</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>In severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia</td>
<td>Hypoxemia</td>
<td>Hypercapnea</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td></td>
<td>Acidosis</td>
<td>Acidosis</td>
<td>Hypercapnea</td>
</tr>
<tr>
<td></td>
<td>PPHN</td>
<td>PPHN</td>
<td>PPHN</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax</td>
<td>Pneumomediastinum</td>
<td>Chemical pneumonitis</td>
</tr>
<tr>
<td></td>
<td>Secondary surfactant inhibition</td>
<td>Respiratory failure</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognosis</th>
<th>RDS</th>
<th>TTN</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent on GA at birth and severity of underlying lung disease; long-term risks of chronic lung disease</td>
<td>Recovery usually expected in 24-72 h</td>
<td>Dependent on severity, mortality up to 20%</td>
<td></td>
</tr>
</tbody>
</table>

PNEUMONIA
- see Pediatric Respiratory, P90
- consider in infants with prolonged or premature rupture of membranes, maternal fever, or if mother is GBS positive
- suspect if infant exhibits respiratory distress, temperature instability, or WBC is low, elevated, or left-shifted
- symptoms may be non-specific
- CXR: hazy lung and/or distinct infiltrates (may be difficult to differentiate from RDS)

Retinopathy of Prematurity
- see Ophthalmology, OP41

Sepsis in the Neonate

Table 33. Sepsis Considerations in the Neonate

<table>
<thead>
<tr>
<th>Early Onset (&lt;72 h)</th>
<th>Late Onset (72 h – 28 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical transmission, 95% present within 24 h after birth</td>
<td>Acquired after birth</td>
</tr>
<tr>
<td>Risk factors:</td>
<td>Most common in preterm infants in NICU (most commonly due to coagulase negative Staphylococcus)</td>
</tr>
<tr>
<td>Maternal infection: UTI, GBS positive, previous child with GBS sepsis or meningitis</td>
<td>Other pathogens implicated include GBS, anaerobes, E. coli, Klebsiella</td>
</tr>
<tr>
<td>Maternal fever/leukocytosis/chorioamnionitis</td>
<td></td>
</tr>
<tr>
<td>Prolonged rupture of membranes (&gt;18 h)</td>
<td></td>
</tr>
<tr>
<td>Preterm labor</td>
<td></td>
</tr>
<tr>
<td>Pathogen: GBS, E. coli, Listeria most common</td>
<td></td>
</tr>
<tr>
<td>Pneumonia more common with early onset sepsis</td>
<td></td>
</tr>
</tbody>
</table>

Signs of Sepsis
- no reliable absolute indicator of occult bacteremia in infants <3 mo, most specific result has been WBC <5
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distension, diarrhea
- hypotonia, seizures, lethargy
- jaundice, hepatomegaly, petechiae, purpura
### Skin Conditions of the Neonate

<table>
<thead>
<tr>
<th>Neonatal Skin Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Response (Cutis Marmorata, Acrocyanosis)</td>
<td>Transient mottling when exposed to cold; usually normal, particularly if premature</td>
</tr>
<tr>
<td>Vernix Caseosa</td>
<td>Soft, creamy, white layer covering baby at birth</td>
</tr>
<tr>
<td>Congenital Dermal Melanocytosis ('Mongolian Spots')</td>
<td>Slate gray macules over lower back and buttocks (may look like bruises); common in dark skinned infants</td>
</tr>
<tr>
<td>Capillary Hemangioma</td>
<td>Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yr, 90% by 9 yr</td>
</tr>
<tr>
<td>Erythema Toxicum</td>
<td>Yellow-white papules surrounded by erythema, eosinophils within the lesions; common rash, resolves by 2 wk</td>
</tr>
<tr>
<td>Milia</td>
<td>Lesions 1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolving</td>
</tr>
<tr>
<td>Pustular Melanosis</td>
<td>Brown macular base with pustules, seen more commonly in African American infants; may be present at birth</td>
</tr>
<tr>
<td>Nevus Simplex (Salmon Patch)</td>
<td>Transient macular vascular malformation of the eyelids and/or neck ('Angel Kiss' or 'Stork Bite'); most lesions disappear by 1 yr of life</td>
</tr>
<tr>
<td>Neonatal Acne</td>
<td>Inflammatory papules and pustules mainly on face; self-resolving</td>
</tr>
</tbody>
</table>

### Fluids and Electrolytes

#### Approach to Infant/Child with Dehydration

**Etiology**
- decreased intake: poor oral intake during acute illness, breastfeeding difficulties, eating disorders
- increased losses: common sites include GI tract (diarrhea, vomiting, bleeding), skin/mucous membranes (fever, burns, hemorrhage, stomatitis), urine (osmotic diuresis [e.g. hyperglycemia, DKA], diuretic therapy, DI, post-obstructive/post ATN recovery diuresis), and respiratory tract (tachypnea, bronchiolitis, pneumonia)

**Management**
- if suspect dehydration based on history (acute illness, decreased number of wet diapers, lethargy, changes in mental status, increased thirst, etc.), you must:

1. **Determine degree of extracellular volume contraction**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 yr</td>
<td>5%*</td>
<td>10%*</td>
</tr>
<tr>
<td>&gt;2 yr</td>
<td>3%*</td>
<td>6%*</td>
</tr>
</tbody>
</table>

   - **Pulse**
     - Normal, full
     - Rapid
   - **Blood Pressure**
     - Normal
     - Low to normal
     - Decreased in shock (very late finding in pediatrics and very dangerous)
   - **Urine Output**
     - Decreased
     - Markedly decreased
     - Anuria
   - **Oral Mucosa**
     - Slightly dry
     - Dry
     - Perched
   - **Anterior Fontanelle**
     - Normal
     - Sunken
     - Markedly sunken
   - **Eyes**
     - Normal
     - Sunken
     - Markedly sunken
   - **Skin Turgor**
     - Normal
     - Decreased
     - Tenting
   - **Capillary Refill**
     - Normal (<3 s)
     - Normal to increased
     - Increased (>3 s)

* Note that percentages refer to percent loss of pre-illness body weight

2. **Determine the likely electrolyte disturbance**
   - dependent on etiology of dehydration and type of fluid loss (isotonic vs. hypertonic vs. hypotonic)

#### Electrolyte Concentrations of Na⁺ and K⁺ (in mEq/L)

<table>
<thead>
<tr>
<th></th>
<th>ICF</th>
<th>ECF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>10</td>
<td>140</td>
</tr>
<tr>
<td>Potassium</td>
<td>150</td>
<td>4</td>
</tr>
</tbody>
</table>

**Assessment of Severity of Dehydration**

- C BASE H₂O
- Capillary refill
- BP
- Anterior fontanelle
- Skin turgor
- Eyes sunken
- HR
- Oral mucosa
- Output of urine
Table 36. Electrolyte Content of Various Bodily Fluids

<table>
<thead>
<tr>
<th>Bodily Fluid</th>
<th>Na⁺ (mmol/L)</th>
<th>K⁺ (mmol/L)</th>
<th>Cl⁻ (mmol/L)</th>
<th>HCO₃⁻ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>30-80</td>
<td>20</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Gastric Juice</td>
<td>60-80</td>
<td>15</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic Juice</td>
<td>140</td>
<td>5-10</td>
<td>60-90</td>
<td>40-100</td>
</tr>
<tr>
<td>Bile</td>
<td>140</td>
<td>5-10</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>140</td>
<td>20</td>
<td>100</td>
<td>25-50</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>75</td>
<td>30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Sweat</td>
<td>20-70</td>
<td>5-10</td>
<td>40-60</td>
<td>0</td>
</tr>
</tbody>
</table>

- for moderate and severe dehydration, initial investigations should include urinalysis and blood work examining electrolyte (Na⁺, K⁺, Cl⁻), glucose, and acid-base (blood pH, pCO₂, HCO₃⁻ disturbances), and impaired renal function (creatinine, BUN)

3) Determine if the child requires PO or IV rehydration
- dehydrated child must receive adequate fluid management, including replacement of ongoing losses and maintenance fluids
- initial management using ORT advantages: ↓ cost, no IV needed, incidence of iatrogenic hyper/ hyponatremia, parental involvement in therapy
- indications for IV rehydration therapy: severe dehydration requiring close monitoring and frequent assessment of electrolytes, inability to tolerate ORT (e.g. vomiting, alteration in mental status, ileus, monosaccharide malabsorption, etc.), inability to provide ORT, failure of ORT in providing adequate rehydration (e.g. persistent diarrhea or vomiting)

4) Return the child to a normal volume and electrolyte status by replacing current deficits and ongoing losses

Figure 15. Algorithm for deficit replacement and replacement of ongoing losses in the dehydrated child

5) Provide the appropriate fluid and electrolyte maintenance daily requirements

Table 37. Maintenance Fluid Requirements

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>100:50:20 Rule (24 h maintenance fluids)</th>
<th>4:2:1 Rule (hourly rate of maintenance fluids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 kg</td>
<td>100 cc/kg/d</td>
<td>4 cc/kg/h</td>
</tr>
<tr>
<td>11-20 kg</td>
<td>50 cc/kg/d</td>
<td>2 cc/kg/h</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>20 cc/kg/d</td>
<td>1 cc/kg/h</td>
</tr>
</tbody>
</table>

- types of fluids used: NS, RL, half NS (0.45% NaCl), 0.2% NS (for neonates only), D5W, and D10W (for neonates only); add potassium chloride if hypokalemic
- in children, all maintenance fluids should have a dextrose component due to their higher risk of hypoglycemia, especially if they are NPO
- common IV fluid combinations used in pediatrics
  - first month of life: D5W/0.2 NS + KCl 20 mEq/L (only add KCl if voiding well)
  - children: D5W/NS + KCl 20 mEq/L or D5W/0.45 NS + KCl 20 mEq/L
  - NS: as bolus to restore circulation in dehydrated children (remains almost entirely distributed in intravascular space)

Special Consideration – SIADH
Clinical Signs: hyponatremia and excretion of concentrated urine
Renal Failure: certain medications (e.g. morphine), post-operative, pain, N/V, pulmonary disease (e.g. pneumonia), CNS disease (e.g. meningitis)
Caution: acute hyponatremia is associated with rapid administration of hypotonic IV, this can lead to cerebral edema and herniation
• most important thing to remember when correcting Na aberrations due to fluid deficits
  ▪ risk of cerebral edema with rapid rehydration with hypotonic or isotonic solutions (i.e. NS),
  therefore replace fluid slowly with close monitoring; aim to adjust (increase or decrease)
  plasma [Na+] by no more than 12 mmol/L/d
  ▪ management depends on etiology, severity of symptoms, and timing (acute vs. chronic)

6) Continue to monitor fluid and electrolyte status
• accurate monitoring of daily fluid intake (PO and IV) and ongoing losses (urine output, 
diarrhea, emesis, drains)
• if child receiving >50% of maintenance fluids through IV, serum electrolyte values should be 
monitored daily and therapy adjusted accordingly
• avoid iatrogenic hyper/hyponatremia, keep the possibility of SIADH in mind

Nephrology

Common Pediatric Renal Diseases

Table 38. Common Manifestations of Renal Disease

<table>
<thead>
<tr>
<th>Neonate</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>flank mass</td>
<td>Hydronephrosis, polycystic disease (autosomal dominant or recessive subtypes), tumor</td>
</tr>
<tr>
<td>hematuria</td>
<td>Renal vein thrombosis, asphyxia, malformation, trauma</td>
</tr>
<tr>
<td>anuria/oliguria</td>
<td>Bilateral renal agenesis, obstruction, asphyxia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child and Adolescent</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>cola/red-colored urine</td>
<td>Acute GN (post-streptococcal, HSP, IgA nephropathy, etc.), hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis)</td>
</tr>
<tr>
<td>gross hematuria</td>
<td>Urologic disease (nephrolithiasis, trauma, etc.), UTI, acute GN</td>
</tr>
<tr>
<td>edema</td>
<td>Nephrotic syndrome, nephritis, acute/chronic renal failure, consider cardiac or liver disease</td>
</tr>
<tr>
<td>HTN</td>
<td>GN, renal failure, dysplasia (consider coarctation, drugs, endocrine causes)</td>
</tr>
<tr>
<td>polyuria</td>
<td>DM, central and nephrogenic DI, renal Fanconi’s syndrome (genetic/metabolic/acquired causes), hypercalcinemia, polyuric renal failure (renal dysplasia)</td>
</tr>
<tr>
<td>proteinuria</td>
<td>Orthostatic, nephrotic syndrome (MCD, etc.), GN</td>
</tr>
<tr>
<td>oliguria</td>
<td>Dehydration, ATN, interstitial nephritis, acute or chronic kidney disease (i.e. renal failure)</td>
</tr>
<tr>
<td>urgency</td>
<td>UTI, vulvovaginitis</td>
</tr>
</tbody>
</table>

Hemolytic Uremic Syndrome

Definition
• simultaneous occurrence of the triad of 1) non-immune microangiopathic hemolytic anemia, 2) 
thrombocytopenia, and 3) acute renal injury

Epidemiology
• annual incidence of 1-2 per 100,000 in Canada
• most common cause of acute renal failure in children

Etiology
• diarrhea positive HUS: 90% of pediatric HUS from E. coli O157:H7, shiga toxin, or verotoxin
• diarrhea negative HUS: other bacteria, viruses, familial, drugs, familial/genetic

Pathophysiology
• toxin binds, invades, and destroys colonic epithelial cells, causing bloody diarrhea
• toxin enters the systemic circulation, attaches, and injures endothelial cells (especially 
in kidney), causing a release of endothelial products (e.g. von Willebrand factor, platelet 
aggregating factor)
• platelet/fibrin thrombi form in multiple organ systems (e.g. kidney, pancreas, brain, etc.) 
resulting in thrombocytopenia
• RBCs are forced through occluded vessels, resulting in fragmented RBCs (schistocytes) that are 
removed by the reticuloendothelial system (hemolytic anemia)
History and Physical Exam
• history: initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea; within 5-7 d begins to show signs of anemia, thrombocytopenia, and renal insufficiency
• physical exam: pallor, jaundice (hemolysis), edema, petechiae, HTN

Investigations
• CBC (anemia, thrombocytopenia), blood smear (schistocytes), electrolytes, renal function, urinalysis (microscopic hematuria), stool cultures, and verotoxin/shigella toxin assay

Management
• mainly supportive: nutrition, hydration, ventilation (if necessary), blood transfusion for symptomatic anemia
• monitor electrolytes and renal function: dialysis if electrolyte abnormality (hyperkalemia) cannot be corrected, fluid overload, or uremia
• steroids are not helpful
• antibiotics are contraindicated because death of bacteria leads to increased toxin release and worse clinical course

Prognosis
• 5-10% mortality, 10-30% long-term renal damage (HTN, proteinuria, decreased renal function)

Nephritic Syndrome

Definition
• acute or chronic syndrome affecting the kidney, characterized by glomerular injury and inflammation, and defined by hematuria (>5 RBCs per high-powered microscope field) and the presence of dysmorphic RBCs and RBC casts on urinalysis
• often accompanied by at least one of proteinuria (<50 mg/kg/d), edema, HTN, azotemia, and oliguria

Epidemiology
• highest incidence in children aged 5-15 yr old

Etiology
• humoral immune response to a variety of etiologic agents → immunoglobin deposition
→ complement activation, leukocyte recruitment, release of growth factors/cytokines → glomerular inflammation and injury → porous podocytes → hematuria + RBC casts ± proteinuria
• HTN secondary to fluid retention and increased renin secretion by ischemic kidneys

Table 39. Major Causes of Nephritic Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Decreased C3</th>
<th>Normal C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (idiopathic)</td>
<td>Post-infectious GN (most common cause of acute GN in pediatrics)</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td></td>
<td>Membranoproliferative</td>
<td>Idiopathic rapidly progressive GN</td>
</tr>
<tr>
<td></td>
<td>• Type I (50-80%)</td>
<td>Anti-GBM disease</td>
</tr>
<tr>
<td></td>
<td>• Type II (&gt; 80%)</td>
<td></td>
</tr>
<tr>
<td>Secondary (systemic disease)</td>
<td>SLE</td>
<td>HSP (very common)</td>
</tr>
<tr>
<td></td>
<td>Bacterial endocarditis</td>
<td>Polyaertinitis nodosa</td>
</tr>
<tr>
<td></td>
<td>Abscess or short nephritis</td>
<td>Granulomatosis with polyangitis</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulinemia</td>
<td>Goodpasture’s syndrome</td>
</tr>
</tbody>
</table>

Risk Factors
• see Major Causes of Nephritic Syndrome, above

History and Physical Exam
• often asymptomatic; some overlap in clinical findings for nephritic and nephrotic syndrome
• gross hematuria, mild-moderate edema, oliguria, HTN
• signs and symptoms suggestive of underlying systemic causes (e.g. fever, arthralgias, rash, dyspnea, pulmonary hemorrhage)

Investigations
• urine
  ▪ dipstick (hematuria, 0 to 2+ proteinuria) and microscopy (>5 RBCs per high-powered microscope field, acanthocytes, RBC casts)
  ▪ first morning urine protein/creatinine ratio (<200 mg/mmol)
• blood work
  ▪ impaired renal function (↑ Cr and BUN) resulting in ↓ pH and electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia)
  ▪ mild anemia on CBC (secondary to hematuria)
  ▪ hypoalbuminemia (secondary to proteinuria)
  ▪ appropriate investigations to determine etiology: C3/C4 levels, serologic testing for recent streptococcal infection (ASOT, anti-hyaluronidase, anti-streptokinase, anti-NAD, anti-DNAse B), ANA, anti-DNA antibodies, ANCA, serum IgA levels, anti-GBM antibodies
• renal biopsy should be considered only in the presence of acute renal failure, no evidence of streptococcal infection, normal and C3/C4

Management
• treat underlying cause
• symptomatic
  ▪ renal insufficiency: supportive (dialysis if necessary), proper hydration
  ▪ HTN: salt and fluid restriction (but not at expense of renal function), ACE inhibitors or ARBs for chronic persistent HTN (not acute cases because ACE inhibitors or ARBs may decrease GFR further)
  ▪ edema: salt and fluid restriction, possibly diuretics (avoid if significant intravascular depletion)
• corticosteroids if indicated: IgA nephropathy, lupus nephritis, etc.

Prognosis
• dependent on underlying etiology
• complications include HTN, heart failure, pulmonary edema, chronic kidney injury (requiring renal transplant)

**Nephrotic Syndrome**

Definition
• clinical syndrome affecting the kidney, characterized by significant proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia

Epidemiology
• highest incidence in children 2-6 yr old, M>F

Etiology
• primary (idiopathic): nephrotic syndrome in the absence of systemic disease (most common cause in pediatrics)
  ▪ glomerular inflammation ABSENT on renal biopsy: MCD (85%), focal segmental glomerular sclerosis
  ▪ glomerular inflammation PRESENT on renal biopsy: membranoproliferative GN, IgA nephropathy
• secondary: nephrotic syndrome associated with systemic disease or due to another process causing glomerular injury (<10% in pediatrics)
  ▪ autoimmune: SLE, DM, rheumatoid arthritis
  ▪ genetic: sickle cell disease, Alport syndrome
  ▪ infections: hepatitis B/C, post-streptococcal, infective endocarditis, HUS, HIV
  ▪ malignancies: leukemia, lymphoma
  ▪ medications: captopril, penicillamine, NSAIDs, antiepileptics
  ▪ vasculitides: HSP, granulomatosis with polyangiitis
• congenital: congenital nephropathy of the Finnish type, Denys-Drash syndrome, etc.

Risk Factors
• family history, certain systemic illnesses and medications (as per Etiology)

History and Physical Exam
• non-specific (e.g. irritability, malaise, fatigue, anorexia, diarrhea)
• edema
  ▪ often first sign; detectable when fluid retention exceeds 3-5% of body weight
  ▪ starts periorbital and often pretibial → edematous areas are white, soft, and pitting
  ▪ gravity dependent: periorbital edema ↓ and pretibial edema ↑ over the day
  ▪ anasarca may develop (i.e. marked periorbital and peripheral edema, ascites, pleural effusions, scrotal/labial edema)
• decrease in effective circulating volume (e.g. tachycardia, HTN, oliguria, etc.)
• foamy urine is a possible sign of proteinuria
Investigations

• urine
  - urine dipstick (3 to 4+ proteinuria, microscopic hematuria) and microscopy (oval fat bodies, hyaline casts)
  - first morning urine protein/creatinine ratio (>200 mg/mmol)

• blood work
  - diagnostic: hypoalbuminemia (<25 g/L), hyperlipidemia/hypercholesterolemia (total cholesterol >5 mmol/L)
  - secondary: electrolytes (hypocalcemia, hyperkalemia, hyponatremia), renal function (↑ BUN and Cr), coagulation profile (↑ PTT)
  - appropriate investigations to rule out secondary causes: CBC, blood smear, C3/C4, ANA, hepatitis B/C titers, ASOT, HIV serology, etc.

• consider renal biopsy if: HTN, gross hematuria, ↓ renal function, low serum C3/C4, no response to steroids after 4 wk of therapy, frequent relapses (>2 in 6 mo), presentation before first year of life (high likelihood of congenital nephrotic syndrome), presentation ≥12 yr (rule out more serious renal pathology than MCD)

Management

• MCD: oral prednisone 2 mg/kg/d (or equivalent) for up to 12 wk → varicella status should be known before starting
• consider cytotoxic agents, immunomodulators, or high-dose pulse corticosteroid if steroid resistant
• symptomatic
  - edema: salt and fluid restriction, possibly diuretic (avoid if significant intravascular depletion); furosemide + albumin for anasarca
  - hyperlipidemia: generally resolves with remission; limit dietary fat intake; consider statin therapy if persistently nephrotic
  - hypoalbuminemia: IV albumin and furosemide not routinely given; consider if refractory edema
  - abnormal BP: control BP; fluid resuscitation if severe intravascular depletion; ACEI or ARBs for persistent HTN
• diet: no added salt; monitor caloric intake and supplement with Ca²⁺ and Vit D if on corticosteroids
• daily weights and BP to assess therapeutic progress
• secondary infections: treat with appropriate antimicrobials; antibiotic prophylaxis not recommended; pneumococcal vaccine at diagnosis and varicella vaccine after remission; varicella Ig + acyclovir if exposed while on corticosteroids
• secondary hypercoagulability: mobilize, avoid hemoconcentration due to hypovolemia, prompt sepsis treatment; heparin if thrombi occur

Prognosis

• generally good: 80% of children responsive to corticosteroids
• up to 2/3 experience relapse, often multiple times; sustained remission with normal kidney function usually by adolescence
• complications: ↑ risk of infections (spontaneous peritonitis, cellulitis, sepsis); hypercoagulability due to decreased intravascular volume and antithrombin III depletion (PE, renal vein thrombosis); intravascular volume depletion, leading to hypotension, shock, renal failure; side effects of drugs

Hypertension in Childhood

Definition

• HTN: sBP and/or dBP ≥95th percentile for sex, age, and height on ≥3 occasions
• pre-HTN: sBP and/or dBP ≥90th percentile but <95th percentile OR BP ≥120/80 irrespective of age, gender, and height

Table 40. 95th Percentile Blood Pressures (mmHg)

<table>
<thead>
<tr>
<th>Age (Yr)</th>
<th>Female</th>
<th></th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50th Percentile for Height</td>
<td>75th Percentile for Height</td>
<td>50th Percentile for Height</td>
</tr>
<tr>
<td>1</td>
<td>104/58</td>
<td>105/59</td>
<td>102/57</td>
</tr>
<tr>
<td>6</td>
<td>111/73</td>
<td>112/73</td>
<td>114/74</td>
</tr>
<tr>
<td>12</td>
<td>123/80</td>
<td>124/81</td>
<td>123/81</td>
</tr>
<tr>
<td>17</td>
<td>125/84</td>
<td>130/85</td>
<td>136/87</td>
</tr>
</tbody>
</table>

Adapted from: Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents Working Group Report from the National High Blood Pressure Education Program

Long-Term Steroid Use Associations:
- Increased appetite
- Impaired growth
- Behavioral changes
- Risk of infection
- Salt and water retention
- HTN
- Bone demineralization
Epidemiology
• increasing prevalence of both HTN and pre-HTN over the last 25+ yr
• prevalence: 3-5% for HTN, 7-10% for pre-HTN; M>F

Etiology
• primary HTN
  ▪ diagnosis of exclusion
  ▪ most common in older children (≥10 yr), especially if positive family history, overweight, and only mild HTN
  ▪ responsible for ~90% of cases of HTN in adolescents, rarely in young children
• secondary HTN
  ▪ identifiable cause of HTN (most likely etiology depends on age)
  ▪ responsible for majority of childhood HTN
• always consider white coat HTN for all ages

Table 41. Etiology of Secondary HTN by Age Group

<table>
<thead>
<tr>
<th>System</th>
<th>Neonates</th>
<th>1 mo-6 yr</th>
<th>7-12 yr</th>
<th>&gt;13 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine/Metabolic</td>
<td>CAH</td>
<td>Wilms’ tumor (↑ renin)</td>
<td>Endocrinopathies*</td>
<td>Endocrinopathies*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroblastoma (↑ catecholamines)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Congenital renal disease</td>
<td>Renal parenchymal disease</td>
<td>Renal parenchymal disease</td>
<td>Renal parenchymal disease</td>
</tr>
<tr>
<td>Vascular</td>
<td>Coarctation of the aorta</td>
<td>Renal artery thrombosis</td>
<td>Coarctation of the aorta</td>
<td>Renovascular abnormalities</td>
</tr>
<tr>
<td>Drugs</td>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Cyclosporine and tacrolimus</td>
<td>OCP</td>
<td>OCP</td>
<td>Cyclosporine and tacrolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal parenchymal disease</td>
<td>Renovascular abnormalities</td>
<td>Recreational drugs</td>
</tr>
</tbody>
</table>

*Note: may include hyperthyroidism, hyperparathyroidism, Cushing’s syndrome, primary hyperaldosteronism/Conn’s syndrome, pheochromocytoma

Risk Factors
• primary HTN: male gender, positive family history, metabolic syndrome, obstructive sleep apnea, African American, prematurity/LBW
• secondary HTN: history of renal disease, abdominal trauma, family history of autoimmune diseases, umbilical artery catheterization

History
• often asymptomatic, but can include FTT, fatigue, epistaxis
• symptoms of hypertensive emergency
  ▪ neurologic: headache, seizures, focal complaints, change in mental status, visual disturbances
  ▪ cardiovascular: symptoms of MI or heart failure (chest pain, palpitations, cough, SOB)
• symptoms of secondary HTN: guided by etiology; ask about medications and recreational drugs (current and past)

Physical Exam
• BP measurement (make sure correct cuff size is used), plot on growth chart, BMI
• look for signs of hypertensive emergency (e.g. full neurologic exam, opthalmoscopy, precordial exam, peripheral pulses, perfusion status)
• look for signs of secondary HTN

Investigations
• laboratory
  ▪ urine dipstick for hematuria and/or proteinuria (renal disease), urine catecholamines (pheochromocytoma, neuroblastoma)
  ▪ blood work: renal function tests (electrolytes, Cr, BUN), consider renin and aldosterone levels (RAS, Conn’s syndrome, Wilms’ tumor)
  ▪ other specific hormones if indicated on history and physical
  ▪ imaging: Echo (coarctation, heart function), abdominal U/S (RAS, abdominal mass), renal radionuclide imaging (renal scarring)
  ▪ other: ocular exam

Management
• treat underlying cause
• non-pharmacologic: modify concurrent cardiovascular risk factors (weight reduction, exercise, salt restriction, smoking cessation)
• pharmacologic: gradual lowering of BP using thiazide diuretics; no antihypertensives have been formally studied in children; if hypertensive emergencies use hydralazine, labetalol, sodium nitroprusside

Pediatric BP Calculation
sBP = age x 2 + 90
dBP = 2/3 x sBP

Signs of Secondary HTN
• Edema (renal parenchymal disease)
• Abdominal or renal bruit (RAS)
• Differential 4 limb BP/diminished femoral pulses (coarctation)
• Abdominal mass (Wilms’, neuroblastoma)
• Goiter/skin changes (hyperthyroidism)
• Ambiguous genitalia (CAH)
• management of end-organ damage (e.g. retinopathy, LVH)
• consider referral to specialist

Prognosis
• end-organ damage (similar to adults) including LVH, CHF, cerebrovascular insults, renal disease, retinopathy

Neurology

Seizure Disorders

• see Neurology, N16

Differential Diagnosis of Seizures in Children
• benign febrile seizure
• CNS: infection, tumor, HIE, trauma, hemorrhage
• metabolic: hypoglycemia, hypocalcemia, hyponatremia
• idiopathic epilepsy and epileptic syndromes
• others: neurocutaneous syndromes, AVM, drug ingestions/withdrawal
• seizure mimics

Investigations
• lab tests: CBC, electrolytes, calcium, magnesium, glucose
• toxicology screen if indicated
• EEG
• CT/MRI, if indicated (focal neurological deficit or has not returned to baseline several hours after seizure)
• consider LP if first-time non-febrile seizure (not indicated for determining recurrence risk of benign febrile seizures or to determine seizure type or epileptic syndrome)

CHILDHOOD EPILEPTIC SYNDROMES

Infantile Spasms
• brief, repeated symmetric contractions of neck, trunk, extremities (flexion and extension) lasting 10-30 s
• occur in clusters; often associated with developmental delay; onset 4-8 mo
• 20% unknown etiology (usually good response to treatment); 80% due to metabolic or developmental abnormalities, encephalopathies, or are associated with neurocutaneous syndromes (usually poor response to treatment)
• can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hyperarrhythmia) or Lennox-Gastaut (see below)
• typical EEG: hyperarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
• management: ACTH, vigabatrin, benzodiazepines

Lennox-Gastaut
• characterized by triad of 1) multiple seizure types, 2) diffuse cognitive dysfunction, and 3) slow generalized spike and slow wave EEG
• onset commonly 3-5 yr of age
• seen with underlying encephalopathy and brain malformations
• management: valproic acid, benzodiazepines, and ketogenic diet; however, response often poor

Juvenile Myoclonic Epilepsy (Janz Syndrome)
• myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
• adolescent onset (12-16 yr of age); autosomal dominant with variable penetrance
• typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
• management: lifelong treatment (valproic acid); excellent prognosis

Childhood Absence Epilepsy
• multiple daily absence seizures lasting <30 s without post-ictal state that may resolve spontaneously or become generalized in adolescence
• peak age of onset 6-7 yr, F>M, strong genetic predisposition
• typical EEG: 3 Hz spike and wave
• management: valproic acid or ethosuximide

Heart problems, such as long QT syndrome and hypertrophic cardiomyopathy, are often misdiagnosed as epilepsy. Include cardiac causes of syncope in your differential diagnosis, particularly when the episodes occur during physical activity.

Seizure Mimics
• Benign paroxysmal vertigo
• Breath holding
• Hypoglycemia
• Narcolepsy
• Night terror
• Pseudoseizure
• Syncope
• Tic

Ketogenic Diet and Other Dietary Treatments for Epilepsy
Cochrane DB Syst Rev 2012;3:CD001903
Study: Systematic review of all studies of ketogenic and related diets. Included the review of 4 RCTs, 6 prospective studies, and 5 retrospective studies.
Population: Adults and children with diagnosed epilepsy of any type.
Intervention: Ketogenic diet, control (placebo diet, any treatment with known antiepileptic properties).
Main Outcome Measure: Seizure control at 3, 6, 12 mo.
Results: Studies showed a response rate of at least 30-50% seizure reduction at 3 mo. This response was maintained for up to a year. A range of side effects were reported. The most frequent were gastrointestinal effects (30%).
Conclusion: The ketogenic diet is a valid option for people with medically-intractable epilepsy.
Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes
- focal motor seizures involving tongue, mouth, face, upper extremity usually occurring in sleep-wake transition states; remains conscious, but aphasic post-ictally
- onset peaks at 5-10 yr of age; 16% of all non-febrile seizures; remits spontaneously in adolescence without sequelae
- typical EEG: repetitive spikes in centrotemporal area with normal background
- management: frequent seizures controlled by carbamazepine, no medication if infrequent seizures

General Approach to Treatment
- education for patient and parents including education and precautions in daily life (e.g. buddy system, showers instead of baths)
- medication
  - initiate: treatment with drug appropriate to seizure type; often if >2 unprovoked afebrile seizures within 6-12 mo
  - optimize: start with one drug and increase dosage until seizures controlled
  - if no effect, switch over to another before adding a second antiepileptic drug
  - continue antiepileptic drug therapy until patient free of seizures for >2 yr, then wean over 4-6 mo
- ketogenic diet (high fat diet): used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

Generalized and Partial Seizures
- see Neurology, N16

Febrile Seizures

Epidemiology
- most common cause of seizure in children (3-5% of children)
- M>F; age 6 mo-6 yr

Clinical Presentation
- often with associated illness or fever and family history
- no evidence of CNS infection/inflammation before or after seizure; no history of non-febrile seizures

Table 42. Comparison of Typical and Atypical Febrile Seizures

<table>
<thead>
<tr>
<th>Simple/Typical (70-80%)</th>
<th>Complex/Atypical (20-30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following:</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td>Duration &lt;15 min (95% &lt; 5 min)</td>
<td>Duration &gt;15 min</td>
</tr>
<tr>
<td>Generalized tonic-clonic</td>
<td>Focal onset or focal features during seizure</td>
</tr>
<tr>
<td>No recurrence in 24 h period</td>
<td>Recurrent seizures (&gt;1 in 24 h period)</td>
</tr>
<tr>
<td>No neurological impairment or developmental delay before or after seizure</td>
<td>Previous neurological impairment or neurological deficit after seizure</td>
</tr>
</tbody>
</table>

Workup
- history: determine focus of fever, description of seizure, medications, trauma history, development, family history
- physical exam: LOC, signs of meningitis, neurological exam, head circumference, focus of infection
- septic workup including LP if suspecting meningitis (strongly consider if child <12 mo; consider if child is 12-18 mo; only if meningeal sign present if child >18 mo)
- if typical febrile seizure, investigations only for determining focus of fever
- EEG/CT/MRI brain not warranted unless atypical febrile seizure or abnormal neurologic findings

Management
- counsel and reassure patient and parents
  - febrile seizures do not cause brain damage
  - very small risk of developing epilepsy: 9% in child with multiple risk factors; 2% in child with typical febrile seizures compared to 1% in general population
  - 33% chance of recurrence (mostly within 1 yr of first seizure and in children <1 yr old)
  - antipyretics and fluids for comfort (though neither prevent seizure)
• prophylaxis with antiepileptic drugs not recommended
• if high risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home
• treat underlying cause of fever

### Recurrent Headache

- see Neurology, N43

**Differential Diagnosis**
- primary headache: tension, migraine, cluster
- secondary headache: see Neurology, N43

**General Assessment**
- if unremarkable history and neurological and general physical exam is negative, most likely diagnosis is migraine or tension headache
- CT or MRI if history or physical reveals red flags
- inquire about level of disability, academic performance, after-school activities

### Hypotonia

- decreased resistance to passive movements – “floppy baby”

**Differential Diagnosis**
- central: chromosomal (DS, Prader-Willi, Fragile X syndrome), metabolic (hypoglycemia, kernicterus), perinatal problems (asphyxia, ICH), endocrine (hypothyroidism, hypopituitarism), systemic illness (TORCH infection, sepsis, dehydration), CNS malformations, dysmorphic syndromes
- peripheral: motor neuron (spinal muscular atrophy, polio), peripheral nerve (Charcot-Marie-Tooth syndrome) neuromuscular junction (myasthenia gravis), muscle fiber (mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

**History and Physical Exam**
- proper assessment of tone requires accurate determination of GA
- differentiate between UMN and LMN lesion: spontaneous posture (spontaneous movement, movement against gravity, frog-leg position); muscle weakness; joint mobility (hyperextensibility); muscle bulk; presence of fasciculations
- postural maneuvers
  - traction response: pull to sit, look for flexion of arms to counteract traction and head lag
  - axillary suspension: suspend infant by holding at axilla and lifting; hypotonic babies will slip through grasp because of low shoulder girdle tone
  - ventral suspension: infant is prone and supported under the abdomen by one hand; infant should be able to hold up extremities; inverted “U” posturing demonstrates hypotonia
- dysmorphic features, cognitive ability, reflexes, strength

**Investigations**
- rule out systemic disorders (e.g. electrolytes, ABG, blood glucose, CK, and serum/urine investigations for multiple etiologies including mitochondrial causes)
- neuroimaging: MRI/MRA when indicated
- EMG, muscle biopsy/NCS
- chromosome analysis, genetic testing, metabolic testing, neuromuscular testing

**Treatment**
- depends on etiology: some treatments available for specific diagnosis
- counsel parents on prognosis and genetic implications
- refer patients for specialized care, refer for rehabilitation, OT, PT, assess feeding ability

### Cerebral Palsy

**Definition**
- a symptom complex, not a disease
- non-progressive central motor impairment syndrome due to insult to or anomaly of the immature CNS
- incidence: 1.5-2.5/1,000 live births (industrialized nations)
- life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion
Etiology

- often obscure, no definite etiology identified in 1/3 of cases
- 10% related to intrapartum asphyxia; 10% due to postnatal insult (infections, asphyxia, prematurity with IVH and trauma)
- association with LBW babies

Clinical Presentation

- general signs: delay in motor milestones, developmental delay, learning disabilities, visual/hearing impairment, seizures, microcephaly, uncoordinated swallow (aspiration)

<table>
<thead>
<tr>
<th>Table 43. Types of Cerebral Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Spastic</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Athetoid/Dyskinetic</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Ataxic</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mixed</td>
</tr>
</tbody>
</table>

Investigations

- may include metabolic screen, chromosome studies, serology, neuroimaging, EMG, EEG (if seizures), ophthalmology assessment, audiology assessment

Treatment

- maximize potential through multidisciplinary services such as primary care physician, OT, PT, SLP, school supports, etc.
- orthopedic management (e.g. dislocations, contractures, rhizotomy)
- management of symptoms: spasticity (baclofen, Botox®), constipation (stool softeners)

Neurocutaneous Syndromes

- characterized by tendency to form tumors of the CNS, PNS, viscera, and skin

NEUROFIBROMATOSIS TYPE I

- autosomal dominant but 50% are the result of new mutations
- also known as von Recklinghausen disease
- incidence 1:3,000, mutation in NF1 gene on 17q11.2 (codes for neurofibromin protein)
- learning disorders, abnormal speech development, and seizures are common
- diagnosis of NF-1 requires 2 or more of
  - ≥6 café-au-lait spots (>5 mm if prepubertal, >1.5 cm if postpubertal)
  - ≥2 neurofibromas of any type or one plexiform neurofibroma
  - ≥2 Lisch nodules (hamartomas of the iris)
  - optic glioma
  - freckling in the axillary or inguinal region
  - a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
  - a first degree relative with confirmed NF-1

NEUROFIBROMATOSIS TYPE II

- autosomal dominant
- incidence 1:33,000
- characterized by predisposition to form intracranial, spinal tumors
- diagnosed when either bilateral vestibular schwannomas are found, or a first-degree relative with NF-2 and either a neurofibroma, meningioma, glioma, or schwannoma is found
- also associated with posterior subcapsular cataracts
- treatment consists of monitoring for tumor development and surgery

In neurocutaneous syndromes, the younger the child at presentation, the more likely they are to develop mental retardation
Respirology

Approach to Dyspnea

- determine if patient is sick or not sick; ABCs
- history: onset, previous episodes, precipitating events, associated symptoms, past medical/family history of respiratory disease
- physical exam: vitals, SpO₂, evidence of cyanosis, respiratory, cardiovascular
- investigations: CBC and differential, electrolytes, BUN, Cr, NP swab, ABG, CXR, ECG (based on clinical findings)

Figure 16. Approach to dyspnea in childhood

Upper Respiratory Tract Diseases

- see Otolaryngology, OT45
- diseases above the thoracic inlet characterized by inspiratory stridor, hoarseness, and suprasternal retraction
- differential diagnosis of stridor: croup, bacterial tracheitis, epiglottitis, foreign body aspiration, subglottic stenosis (congenital or iatrogenic), laryngomalacia/tracheomalacia (collapse of airway cartilage on inspiration)

Table 44. Common Upper Respiratory Tract Infections in Children

<table>
<thead>
<tr>
<th>Croup (Laryngotracheobronchitis)</th>
<th>Bacterial Tracheitis</th>
<th>Epiglottitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subglottic laryngitis</td>
<td>Subglottic tracheitis</td>
<td>Supraglottic laryngitis</td>
</tr>
<tr>
<td>Common in children &lt;6 yr, with peak incidence between 7-36 mo</td>
<td>Rare</td>
<td>Very rare – due to Hib vaccination</td>
</tr>
<tr>
<td>Common in fall and early winter</td>
<td>All age groups</td>
<td>Usually older (2-6 yr)</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parainfluenza (75%)</td>
<td>S. aureus</td>
<td>H. influenzae</td>
</tr>
<tr>
<td>Influenza A and B</td>
<td>H. influenzae</td>
<td>β-hemolytic strep</td>
</tr>
<tr>
<td>RSV</td>
<td>α-hemolytic strep</td>
<td></td>
</tr>
<tr>
<td>Adenovirus</td>
<td>Pneumococcus</td>
<td></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common prodrome: rhinorrhea, pharyngitis, cough ± low-grade fever</td>
<td>Similar symptoms as croup, but more rapid deterioration with high fever</td>
<td>Toxic appearance</td>
</tr>
<tr>
<td>Hoarse voice</td>
<td>Toxic appearance</td>
<td>Rapid progression</td>
</tr>
<tr>
<td>Barking cough</td>
<td>Does not respond to croup treatments</td>
<td>4 Ds – drooling, dysphagia, dysphonia, distress</td>
</tr>
<tr>
<td>Stridor</td>
<td></td>
<td>Stridor</td>
</tr>
<tr>
<td>Worse at night</td>
<td></td>
<td>Tripod position</td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td></td>
<td>Sternal recession</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anxious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fever (&gt;102.2°F/39°C)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>Clinical diagnosis: CXR in atypical presentation: &quot;steeple sign&quot; from subglottic narrowing</td>
<td>Clinical diagnosis</td>
</tr>
<tr>
<td></td>
<td>Clinical diagnosis: Endoscopy: definitive diagnosis</td>
<td>Avoid examining the throat to prevent further respiratory exacerbation</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>No evidence for humidified O₂</td>
<td>Intubation</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone: PO 1 dose</td>
<td>Antibiotics</td>
</tr>
<tr>
<td></td>
<td>Racemic epienphrine: nebulized, 1-3 doses, q1-2h</td>
<td>Prevented with Hib vaccine</td>
</tr>
<tr>
<td></td>
<td>Intubation if unresponsive to treatment</td>
<td></td>
</tr>
</tbody>
</table>
Lower Respiratory Tract Diseases

- obstruction of airways below thoracic inlet, produces more expiratory sounds
- classic symptom: wheezing

Differential Diagnosis of Wheezing
- common: asthma (recurrent wheezing episodes, identifiable triggers, typically over 6 yr), bronchiolitis (first episode of wheezing, usually under 1 yr), recurrent aspiration (often neurological impairment), pneumonia (fever, cough, malaise)
- uncommon: foreign body (acute unilateral wheezing and coughing), CF (prolonged wheezing, unresponsive to therapy), bronchopulmonary dysplasia (often develops after prolonged ventilation in the newborn)
- rare: CHF, mediastinal mass, bronchiolitis obliterans, tracheobronchial anomalies

Pneumonia

Etiology
- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

Clinical Presentation
- incidence is greatest in first year of life with viral causes being most common in children <5 yr
- cough, wheezing, stridor, fever, tachypnea
- CXR: diffuse, streaky infiltrates bilaterally
- bacterial causes may present with cough, fever, chills, dyspnea, more dramatic CXR changes (e.g. lobar consolidation, pleural effusion)

Management
- supportive therapy: hydration, antipyretics, humidified O₂

Table 45. Common Causes and Treatment of Pneumonia at Different Ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Atypical Bacteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>GBS</td>
<td>CMV</td>
<td>Mycoplasma hominis</td>
<td>Ampicillin + gentamicin / tobramycin</td>
</tr>
<tr>
<td></td>
<td>E. coli</td>
<td>Herpes virus</td>
<td>Ureaplasma urealyticum</td>
<td>(add erythromycin if suspect Chlamydia)</td>
</tr>
<tr>
<td></td>
<td>Listeria</td>
<td>Enteroirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3 mo</td>
<td>S. aureus</td>
<td>CMV, RSV</td>
<td>Chlamydia trachomatis</td>
<td>Cefuroxime OR ampicillin + erythromycin OR clarithromycin</td>
</tr>
<tr>
<td></td>
<td>S. pneumonia</td>
<td>RSV, Parainfluenza</td>
<td>Ureaplasma urealyticum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B. pertussis</td>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 mo-5 yr</td>
<td>S. pneumonia</td>
<td>RSV</td>
<td>Mycoplasma pneumoniae</td>
<td>Amoxicillin (if mild) OR amoxicillin OR cefuroxime</td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>Adenovirus</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. influenza</td>
<td>Influenza</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GAS</td>
<td>Varicella</td>
<td>Mycoplasma pneumoniae</td>
<td>Erythromycin OR clarithromycin (1st line) OR ampicillin OR cefuroxime</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adenovirus</td>
<td>Chlamydia pneumoniae</td>
<td></td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>S. pneumonia</td>
<td>Influenza</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>H. influenza</td>
<td>Varicella</td>
<td>Legionella pneumophila</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>Adenovirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bronchiolitis

Definition
- LRTI that has wheezing and signs of respiratory distress

Epidemiology
- the most common LRTI in infants, affects 50% of children in first 2 yr of life; peak incidence at 6 mo, winter or early spring
- increased incidence of asthma in later life

Etiology
- RSV (>50%), parainfluenza, influenza, rhinovirus, adenovirus, M. pneumoniae (rare)

Clinical Presentation
- prodrome of URTI with cough and fever
- feeding difficulties, irritability
- wheezing, crackles, respiratory distress, tachypnea, tachycardia, retractions, poor air entry; symptoms often peak at 3-4 d
Bronchodilators for Bronchiolitis

Cochrane DB Syst Rev 2010;12:CD001266

Study: Meta-analysis of prospective, randomized, double-blinded, placebo-controlled trials.

Patients: 1,912 infants (28 trials) up to 24 mo old with bronchiolitis.

Intervention: Bronchodilators (including albuterol, salbutamol, terbutaline, ipratropium bromide, and adrenergic agents) given oral, subcutaneous, or nebulized vs. placebo.

Main Outcome: Oxygen saturation.

Results: No clinically significant difference for infants treated with bronchodilators vs. placebo for bronchiolitis. Given the costs and side effects, it is not recommended to use bronchodilators as management for bronchiolitis in infants.

Investigations
- CXR (only in severe disease, poor response to therapy, chronic episode): air trapping, peribronchial thickening, atelectasis, increased linear markings
- NP swab: direct detection of viral antigen (immunofluorescence)
- WBC can be normal

Treatment
- self-limiting disease with peak symptoms usually lasting 2-3 wk
- mild to moderate distress
  - supportive: PO or IV hydration, antipyretics for fever, regular or humidified high flow O2
  - severe distress
    - as above + intubation and ventilation as needed
    - consider rebetol (Ribavirin*) in high risk groups: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodefiective
- monthly RSV-Ig or palivizumab (monoclonal antibody against the F-glycoprotein of RSV) is protective against severe disease in high risk groups; case fatality rate <1%
- antibiotics have no therapeutic value unless there is secondary bacterial pneumonia
- indications for hospitalization
  - hypoxia: O2 saturation <92% on initial presentation
  - persistent resting tachypnea >60/min and retractions after several salbutamol masks
  - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
  - young infants <6 mo old (unless extremely mild)
  - significant feeding problems
  - social problem (e.g. inadequate care at home)

Asthma

Definition
- see Respirology, R7
- characterized by recurrent episodes of airway hyperreactivity, bronchospasm, and inflammation; reversible small airway obstruction
- very common, presents most often in early childhood
- associated with other atopic diseases such as allergic rhinitis or atopic dermatitis

Clinical Presentation
- episodic bouts of wheezing, dyspnea, tachypnea, cough (usually at night/early morning, with activity, or cold exposure)
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze

Triggers
- URTI (viral or Mycoplasma), weather (cold exposure, humidity changes), allergens (pets), irritants (cigarette smoke), exercise, emotional stress, drugs (ASA, β-blockers)

Classification
- mild: occasional attacks of wheezing or coughing (<2/wk); symptoms respond quickly to inhaled bronchodilator; never needs systemic corticosteroids
- moderate: more frequent episodes with symptoms persisting and chronic cough; decreased exercise tolerance; sometimes needs systemic corticosteroids
- severe: daily and nocturnal symptoms; frequent ED visits and hospitalizations; usually needs systemic corticosteroids

Management
- acute
  - O2 (keep O2 saturation ≥90%) and fluids if dehydrated
  - β2-agonists: salbutamol (Ventolin®) MDI + spacer 4-8 puffs every 20 min for 3 doses, then every 1-4 h as needed; nebulized 0.15 mg/kg (minimum 2.5 mg) every 20 min for 3 doses then 0.15-0.3 mg/kg every 1-4 h as needed or 0.5 mg/kg continuous nebulization
  - ipratropium bromide (Atrovent®) if severe: MDI + spacer, 4-8 puffs every 20 min as needed up to 3 h; nebulized 0.25-0.5 mg every 20 min for 3 doses, then as needed
  - steroids: prednisone (1-2 mg/kg x 5 d) or dexamethasone (0.3 mg/kg/d x 5 d or 0.6 mg/kg/d x 2 d); in severe disease, use IV steroids
  - continue to observe; can discharge patient if asymptomatic for 2-4 h after last dose
- chronic
  - step-wise approach for management for ages 0-11: ≥12 yr follow adult guidelines
  - step 1 for intermittent asthma; steps 2-6 for persistent asthma requiring daily medication (step up or down based on patient's asthma control):
    * step 1: short acting β2-agonists (SABA) PRN

National Heart, Lung, and Blood Institute Guidelines for Well-Controlled Asthma
- Daytime symptoms ≤2 d/wk
- Night time symptoms <1 night/mo
- Normal physical activity
- Mild and infrequent exacerbations
- No work/school absenteeism
- Need for β-agonist ≤2 doses/wk
- FEV1, or peak expiratory flow >80% of personal best
- FEV1/FVC >80%
- Exacerbations requiring oral systemic corticosteroids 0-1/yr

Children with bronchiolitis do not respond to ipratropium bromide (Atrovent®) or steroids

National Heart, Lung, and Blood Institute Guidelines for Well-Controlled Asthma
- Daytime symptoms ≤2 d/wk
- Night time symptoms <1 night/mo
- Normal physical activity
- Mild and infrequent exacerbations
- No work/school absenteeism
- Need for β-agonist ≤2 doses/wk
- FEV1, or peak expiratory flow >80% of personal best
- FEV1/FVC >80%
- Exacerbations requiring oral systemic corticosteroids 0-1/yr
step 2: low-dose inhaled corticosteroids (ICS) preferred; alternative: cromolyn or montelukast (or LTRA, nedocromil, or theophylline for ages 5-11)
step 3: medium-dose ICS (OR low-dose ICS + long acting β2-agonist (LABA) for ages 5-11)
step 4: medium-dose ICS + LABA or monteleukast
step 5: high-dose ICS + LABA or monteleukast
step 6: high-dose ICS + LABA or monteleukast + oral systemic corticosteroids
at all steps
patient education, environmental control, management of comorbidities
quick relief medication: SABA as needed
consider injection immunotherapy for steps 2-4

indicators for hospitalization
- decision to hospitalize is based on duration of symptoms, severity of symptoms, severity of obstruction, response to ED treatment, course and severity of previous exacerbations, medication use at time of exacerbation, access to medical care/medications, adequacy of home support, and presence of psychiatric illness
- individualized decision to admit to ward: FEV1 or PEF <70%; ongoing mild-moderate symptoms despite ED treatment
- admit to ICU: FEV1 or PEF <40%, PCO2 ≥ 42 mmHg, physical exam shows severe symptoms, drowsiness, confusion

Cystic Fibrosis
- see Respirology, R12

Etiology
- 1 per 3,000 live births, mostly Caucasians
- autosomal recessive, CFTR gene found on chromosome 7 (ΔF508 mutation in 70%, but >1,600 different mutations identified) resulting in a dysfunctional chloride channel on the apical membrane of cells
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction

Clinical Presentation
- neonatal: meconium ileus, prolonged jaundice, antenatal bowel perforation
- infancy: pancreatic insufficiency with steatorrhea and FTT (despite voracious appetite), anemia, hypoproteinemia, hyponatremia
- childhood: heat intolerance, wheezing or chronic cough, recurrent chest infections (S. aureus, P. aeruginosa, H. influenzae), hemoptysis, nasal polyps, distal intestinal obstruction syndrome, rectal prolapse, clubbing of fingers
- older patients: COPD, infertility (males), decreased fertility (female)

Investigations
- sweat chloride test x 2 (>60 mEq/L)
- false positive tests: malnutrition, atopic dermatitis, hypothyroidism, hypoparathyroidism, GSD, adrenal insufficiency, G6PD, Klinefelter syndrome, technical issues, autonomic dysfunction, familial cholestasis syndrome
- false negative tests: technical problem with test, malnutrition, skin edema, mineralocorticoids

Management
- nutritional counseling: high calorie diet, pancreatic enzyme replacements, fat soluble vitamin supplements
- management of chest disease: physiotherapy, postural drainage, exercise, bronchodilators, aerosolized DNAase and inhaled hypertonic saline, antibiotics (e.g. cephalosporin, cloxacinil, ciprofloxacin, inhaled tobramycin depending on sputum C&S), lung transplantation
- genetic counseling

Complications
- respiratory failure, pneumothorax (poor prognostic sign), cor pulmonale (late), pancreatic fibrosis with DM, gallstones, cirrhosis with portal HTN, infertility (male)
- early death (current median survival in the US is 37.4 yr)
Evaluation of Limb Pain

Table 46. Differential Diagnosis of Limb Pain

<table>
<thead>
<tr>
<th>Cause</th>
<th>&lt;3 yr</th>
<th>3-10 yr</th>
<th>&gt;10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Inflammatory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient synovitis</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>JIA</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SLE</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>HSP</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Anatomic/Orthopedic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legg-Calvé-Perthes disease</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Slipped capital femoral epiphysis</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osgood-Schlatter disease</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bone tumor</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemophilia (hemarthrosis)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Pain Syndromes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Growing pains</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Reflex sympathetic dystrophy</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Must rule out infection, malignancy, and acute orthopedic conditions

History
- Demographics (age, gender)
- Pattern of onset and progression of symptoms (including acuity and chronicity)
- Morning stiffness, limp/weight-bearing status, night pain
- Joint involvement (type, distribution) ± spine (axial) involvement
- Extra-articular manifestations and systemic symptoms
- Functional status – activities of daily living
- Family history (arthritis, IBD, psoriasis, spondyloarthropathies, uveitis, bleeding disorders, sickle cell anemia)
- Past medical illness, intercurrent infection, travel, sick contact history, joint injury

Physical Exam
- Growth parameters
- Screening examination (pediatric gait, arms, legs, spine exam)
- Joint exam: inspection/palpation (swelling, erythema, warmth, tenderness, deformity), ROM
- Adjacent structures (bone, tendon, muscle, skin)
- Leg length
- Neurologic exam

Investigations
- Basic: CBC and differential, blood smear, ESR, CRP, x-ray
- As indicated: blood (ANA, RF, culture, viral/bacterial serology, CK, PTT, sickle cell screen, immunoglobulins, complement), urinalysis, synovial fluid (cell count, Gram stain, culture), TB skin test, imaging, bone marrow aspiration, slit lamp exam

Red Flags for Limb Pain
- Fever, pinpoint pain/tenderness, pain out of proportion to degree of inflammation, night pain, weight loss, erythema
Growing Pains

Epidemiology
• age 2-12 yr, M=F

Clinical Presentation
• diagnosis of exclusion
• intermittent, non-articular pain in childhood with normal physical exam findings
• pain at night, often limited to the calf, shin, or thigh; typically short-lived and bilateral
• relieved by heat, massage, mild analgesics
• child is well, asymptomatic during the day, no functional limitation
• possible family history of growing pains

Management
• lab investigations not necessary if typical presentation; reassurance and supportive management

Transient Synovitis of the Hip

• benign, self-limited disorder, usually occurs after URTI, pharyngitis, AOM

Epidemiology
• age 3-10 yr, M>F

Clinical Presentation
• afebrile or low-grade fever, pain typically occurs in hips, knees (referred from hip); painful limp but full ROM (pain not as pronounced as in joint or bone infections)
• symptoms resolve over 7-10 d

Investigations
• WBC within normal limits; ESR and CRP may be mildly elevated
• joint effusions may be seen on imaging
• diagnosis of exclusion (rule out septic arthritis and osteomyelitis)

Treatment
• symptomatic and anti-inflammatory medications

Septic Arthritis and Osteomyelitis

• MEDICAL EMERGENCY
• see Orthopedics, OR10

Table 47. Microorganisms and Treatment Involved in Septic Arthritis/Osteomyelitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>GBS, <em>S. aureus</em>, Gram negative bacilli, <em>H. influenzae</em></td>
<td>cefazolin + aminoglycoside or cefotaxime</td>
</tr>
<tr>
<td>Infant (1-3 mo)</td>
<td><em>Strep</em>. spp., <em>Staph</em>. spp., <em>H. influenzae</em></td>
<td>cefazolin + cefotaxime</td>
</tr>
<tr>
<td>Child</td>
<td><em>S. aureus</em>, <em>S. pneumoniae</em>, GAS</td>
<td>cefazolin</td>
</tr>
<tr>
<td>Adolescent</td>
<td>As above; also <em>N. gonorrhoeae</em></td>
<td>cefazolin</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>As above; also <em>Salmonella</em></td>
<td>cefotaxime</td>
</tr>
</tbody>
</table>

GAS = group A Strep; GBS = group B Strep
Adapted from: Tse SML, Laxer RM. Pediatrics in Review 2006;27:170-179

Juvenile Idiopathic Arthritis

• a heterogenous group of conditions characterized by persistent arthritis in children <16 yr
• diagnosis: arthritis in ≥1 joint(s); duration ≥6 wk; onset age <16 yr old; exclusion of other causes of arthritis; classification defined by features/number of joints affected in the first 6 mo of onset

Systemic Arthritis (Still’s Disease)
• onset at any age, M=F
• once or twice daily fever spikes (>101.3°F) ≥2 d/wk; children usually acutely unwell during fever episodes
• extra-articular features: erythematous “salmon-colored” maculopapular rash, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia, serositis
• arthritis may occur weeks to months later
• high ESR, CRP, WBC, platelet count

**Oligoarticular Arthritis (1-4 joints)**
- onset early childhood, F>M
- persistent: affects no more than 4 joints during the disease course
- extended: affects more than 4 joints after the first 6 mo
- typically affects large joints: knees > ankles, elbows, wrists; hip involvement unusual
- ANA positive ~60-80%, RF negative
- screening eye exams for asymptomatic anterior uveitis (occurs in ~30%)
- complications: knee flexion contracture, quadriceps atrophy, leg-length discrepancy, growth disturbances

**Polyarticular Arthritis (5 or more joints)**
- RF negative
  - onset: 2-4 yr and 6-12 yr, F>M
  - symmetrical involvement of large and small joints of hands and feet, TMJ, cervical spine
- RF positive
  - onset: late childhood/early adolescence, F>M
  - similar to the aggressive form of adult rheumatoid arthritis
  - severe, rapidly destructive, symmetrical arthritis of large and small joints
  - may have rheumatoid nodules at pressure points (elbows, knees)
  - unremitting disease, persists into adulthood

**Enthesitis-Related Arthritis**
- onset: late childhood/adolescence, M>F
- arthritis and/or enthesitis (inflammation at the site where tendons or ligaments attach to the bone)
- weight bearing joints, especially hip and intertarsal joints
- risk of developing ankylosing spondylitis in adulthood

**Psoriatic Arthritis**
- onset: 2-4 yr and 9-11 yr, F>M
- arthritis and psoriasis OR arthritis and at least two of
  - dactylitis, nail abnormalities, or family history of psoriasis in a 1st degree relative
  - asymmetric or symmetric small or large joint involvement

**Management**
- goals of therapy: eliminate inflammation, prevent joint damage, promote normal growth and development as well as normal function, minimize medication toxicity
- exercise to maintain ROM and muscle strength
- multidisciplinary approach: OT/PT, social work, orthopedics, ophthalmology, rheumatology
- 1st line drug therapy: NSAIDs, intra-articular corticosteroids
- 2nd line drug therapy: DMARDs (methotrexate, sulfasalazine, leflunamide), corticosteroids (acute management of severe arthritis, systemic symptoms of JIA, topical eye drops for uveitis), biologic agents

**Reactive Arthritis**
- see **Rheumatology**, RH24
- arthritis (typically the knee) follows bacterial infection, especially with *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Chlamydia*, and most commonly *Streptococcus* (post-streptococcal reactive arthritis)
- typically resolves spontaneously
- may progress to chronic illness or Reiter's syndrome (urethritis, conjunctivitis)

**Lyme Arthritis**
- see **Infectious Diseases**, ID23
- caused by spirochete *Borrelia burgdorferi*
- incidence highest among 5-10 yr olds
- do not treat children <8 yr old with doxycycline (may cause permanent tooth discoloration)
Systemic Lupus Erythematosus

- see Rheumatology, RH1
- autoimmune illness affecting multiple organ systems
- incidence 1/1,000, more commonly age >10, F:M = 10:1
- childhood-onset SLE vs. adult-onset SLE: children have more active disease, are more likely to have renal disease, and children receive more intensive drug therapy and have a poorer prognosis

Vasculitides

HENOC-SCHÖNLEIN PURPURA
- most common vasculitis of childhood, peak incidence 4-10 yr, M:F = 2:1
- vasculitis of small vessels
- often have history of URTI 1-3 wk before onset of symptoms

Clinical Presentation
- clinical triad: 1) palpable purpura, 2) abdominal pain, 3) arthritis
- skin: palpable, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthritis involving large joints associated with painful edema
- GI: abdominal pain, GI bleeding, intussusception
- renal: microscopic hematuria, IgA nephropathy, proteinuria, HTN, renal failure in <5%

Management
- mainly supportive
- anti-inflammatory medications for joint pain, corticosteroids for select patients
- monitor for protein on urinalysis every month for 6 mo, checking for renal disease, which may develop late (immunosuppressive therapy if severe)

Prognosis
- self-limited, resolves within 4 wk
- recurrence in about one-third of patients
- long-term prognosis dependent on severity of nephritis

KAWASAKI DISEASE
- acute vasculitis of unknown etiology (likely triggered by infection)
- medium-sized vasculitis with predilection for coronary arteries
- most common cause of acquired heart disease in children in developed countries
- peak age: 3 mo-5 yr; Asians > Blacks > Caucasians

Diagnostic Criteria
- fever persisting ≥5 d AND ≥4 of the following features
  1. bilateral, non-exudative conjunctival injection
  2. oral mucous membrane changes (fissured lips, strawberry tongue, injected pharynx)
  3. changes of the peripheral extremities
    - acute phase: edema of hands, feet, palms, or soles
    - subacute phase: periungual desquamation
  4. polymorphous rash
  5. cervical lymphadenopathy >1.5 cm in diameter (usually unilateral)
- exclusion of other diseases (e.g. scarlet fever, measles)
- atypical Kawasaki disease: fever persisting ≥5 d and 2-3 of the above criteria
  - further evaluation dictated by CRP, ESR, and supplemental laboratory criteria

Management
- high (anti-inflammatory) dose of ASA while febrile
- low (anti-platelet) dose of ASA in subacute phase until platelets normalize, or longer if coronary artery involvement
- IVIg (2 g/kg) within 10 d of onset reduces risk of coronary aneurysm formation
- baseline 2D-Echo and follow up periodic 2D-Echo (usually at 6 wk)

Complications
- coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children, <5% if receive IVIg within 10 d of fever
- 50% of aneurysms regress within 2 yr
- anticoagulation for multiple or large coronary aneurysms
- risk factors for coronary disease: male, age <1 or >9 yr, fever >10 d, Asian or Hispanic ethnicity, thrombocytopenia, hyponatremia
Table 48. Commonly Used Medications in Pediatrics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen (Tylenol®)</td>
<td>10-15 mg/kg/dose q4-6h pm</td>
<td>Analgesic, antipyretic</td>
<td>Not to exceed 60 mg/kg/d in neonates or 75 mg/kg/d in older children to a max of 4 g/d. Causes hepatotoxicity at high doses.</td>
</tr>
<tr>
<td>amoxicillin (Amoxicil®)</td>
<td>80-90 mg/kg/d PO q6h</td>
<td>Otitis media</td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>0.6 mg/kg PO x 1</td>
<td>Croup</td>
<td></td>
</tr>
<tr>
<td>fluticasone (Flovent®)</td>
<td>Moderate dose – 250-500 µg/d divided bid</td>
<td>High dose – ≥ 500 µg/d divided bid</td>
<td>Asthma</td>
</tr>
<tr>
<td>ibuprofen (Advil®)</td>
<td>5-10 mg/kg/dose q6-8h</td>
<td>Analgesic, antipyretic</td>
<td>Cautious use in patients with liver impairment, history of GI bleeding or ulcers</td>
</tr>
<tr>
<td>iron</td>
<td>6 mg/kg/d elemental iron OD or divided tid</td>
<td>Anemia</td>
<td>SE: dark stool, constipation, dark urine</td>
</tr>
<tr>
<td>omeprazole</td>
<td>GERD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ondansetron</td>
<td>Post-operative N/V</td>
<td>Gastroenteritis</td>
<td>SE: Qtc prolongation, orally disintegrating tablets contain phenylalanine (caution in PKU patients)</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>3-5 mg/kg/d PO or bid</td>
<td>Seizures</td>
<td>SE: CNS depression</td>
</tr>
<tr>
<td>polyethylene glycol 3350 (PEG)</td>
<td>Discontinuation: 1-1.5 g/kg/d x 3 d</td>
<td>Maintenance: starting dose at 0.4-1 g/kg</td>
<td></td>
</tr>
<tr>
<td>prednisone/</td>
<td>1-2 mg/kg/d PO x 5 d</td>
<td>Asthma</td>
<td>Oral prednisone is bitter tasting, consider using prednisolone</td>
</tr>
<tr>
<td>prednisolone</td>
<td>3.4 mg/kg/d PO then taper to 1-2 mg/kg/d</td>
<td>ITP, Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
<td>salbutamol (Ventolin®)</td>
<td>0.01-0.03 mL/kg/dose in 3 mL NS via nebulizer q6-8h pm</td>
<td>Acute asthma</td>
<td>Can cause tachycardia, hypokalemia, restlessness</td>
</tr>
<tr>
<td>omeprazole</td>
<td>0.3 mg/kg/d PO divided q8h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>prednisilone/</td>
<td>3-4 mg/kg/d PO then taper to 1-2 mg/kg/d</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
<tr>
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<td>0.01-0.03 mL/kg/dose in 3 mL NS via nebulizer q6-8h pm</td>
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<td>SE: dark stool, constipation, dark urine</td>
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<td>ondansetron</td>
<td>Post-operative N/V</td>
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<td>SE: Qtc prolongation, orally disintegrating tablets contain phenylalanine (caution in PKU patients)</td>
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<tr>
<td>phenobarbital</td>
<td>3-5 mg/kg/d PO or bid</td>
<td>Seizures</td>
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<td>Discontinuation: 1-1.5 g/kg/d x 3 d</td>
<td>Maintenance: starting dose at 0.4-1 g/kg</td>
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<td>prednisone/</td>
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<td>Can cause tachycardia, hypokalemia, restlessness</td>
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<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>ankle-brachial index</td>
</tr>
<tr>
<td>APL</td>
<td>abductor pollicis longus</td>
</tr>
<tr>
<td>ATLS</td>
<td>advanced trauma life support</td>
</tr>
<tr>
<td>BMR</td>
<td>basal metabolic rate</td>
</tr>
<tr>
<td>CMC</td>
<td>carpo-metacarpal</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CVD</td>
<td>cerebrovascular disease</td>
</tr>
<tr>
<td>DSW</td>
<td>5% dextrose in water</td>
</tr>
<tr>
<td>DEEP</td>
<td>deep inferior epigastric perforator</td>
</tr>
<tr>
<td>DIP</td>
<td>distal interphalangeal joint</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>EMG</td>
<td>electromyography</td>
</tr>
<tr>
<td>ENT</td>
<td>ear, nose, throat</td>
</tr>
<tr>
<td>EGM</td>
<td>extracranial movement</td>
</tr>
<tr>
<td>EPS</td>
<td>extensor pollicis brevis</td>
</tr>
<tr>
<td>FDP</td>
<td>flexor digitorum profundus</td>
</tr>
<tr>
<td>FDS</td>
<td>flexor digitorum superficialis</td>
</tr>
<tr>
<td>FTSG</td>
<td>full thickness skin graft</td>
</tr>
<tr>
<td>GBS</td>
<td>group B Streptococcus</td>
</tr>
<tr>
<td>IGB</td>
<td>incision and drainage</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>IGAP</td>
<td>inferior gluteal artery perforator</td>
</tr>
<tr>
<td>IP</td>
<td>interphalangeal</td>
</tr>
<tr>
<td>IVG</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>MC</td>
<td>metacarpal</td>
</tr>
<tr>
<td>MCP</td>
<td>metacarpal phalangeal joint</td>
</tr>
<tr>
<td>NCV</td>
<td>nerve conduction velocity</td>
</tr>
<tr>
<td>NS</td>
<td>normal saline</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>OM</td>
<td>otitis media</td>
</tr>
<tr>
<td>ORIF</td>
<td>open reduction internal fixation</td>
</tr>
<tr>
<td>PIP</td>
<td>proximal interphalangeal joint</td>
</tr>
<tr>
<td>PVD</td>
<td>peripheral vascular disease</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RL</td>
<td>Ringer’s lactate</td>
</tr>
<tr>
<td>ROM</td>
<td>range of motion</td>
</tr>
<tr>
<td>SGAP</td>
<td>superior gluteal artery perforator</td>
</tr>
<tr>
<td>SIAOH</td>
<td>syndrome of inappropriate antidiuretic hormone</td>
</tr>
<tr>
<td>SIEA</td>
<td>superficial inferior epigastric artery</td>
</tr>
<tr>
<td>SLP</td>
<td>speech language pathology</td>
</tr>
<tr>
<td>SOF</td>
<td>superior orbital fissure</td>
</tr>
<tr>
<td>STSG</td>
<td>split thickness skin graft</td>
</tr>
<tr>
<td>TBSA</td>
<td>total body surface area</td>
</tr>
<tr>
<td>TMJ</td>
<td>temporomandibular joint</td>
</tr>
<tr>
<td>TRAM</td>
<td>transverse rectus abdominis myocutaneous</td>
</tr>
<tr>
<td>UCL</td>
<td>ulnar collateral ligament</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
</tr>
</tbody>
</table>

**Basic Anatomy Review**

**Skin**

*Figure 1. Split and full (whole) thickness skin grafts*

**Hand**

**BONES AND NERVES**

*Figure 2. Arterial supply in the hand*

*Figure 3. Carpal bones*

*Figure 4. Sensory distribution in the hand*
TENDONS

Figure 5. Flexor tendon insertion at PIP and DIP

Figure 6. Extensor mechanism of digits

Figure 7. Carpal tunnel

Figure 8. Extensor compartments of the wrist (dorsal view and cross-sectional view)

Carpal Bone Mnemonic
So Scaphoid
Long Lunate
To Triquetrum
Pinky Pisiform
Horse Hamate
Comes Capitate
The Trapezoid
Thumb Trapezium

Flexor Tendons
All require OR repair
Extensor Tendons
ER repair unless proximal/multiple tendons

1. Extensor retinaculum
Compartment 1
2. Abductor pollicis longus
3. Extensor pollicis brevis
Compartment 2
4. Extensor carpi radialis brevis
5. Extensor carpi radialis longus
Compartment 3
6. Extensor pollicis longus
(EPL tendon passes around Lister’s tubercle)
Compartment 4
7. Extensor digitorum
8. Extensor indicis
Compartment 5
9. Extensor digitii minimi
Compartment 6
10. Extensor carpi ulnaris
**Brachial Plexus**

**Figure 9. Brachial plexus anatomy**

<table>
<thead>
<tr>
<th>BRANCHES</th>
<th>CORDS</th>
<th>DIVISIONS</th>
<th>TRUNKS</th>
<th>ROOTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral pectoral</td>
<td>Suprascapular</td>
<td>Superior</td>
<td>Posterior</td>
<td>C4</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>Dorsal scapular</td>
<td>Anterior</td>
<td>Superior</td>
<td>C5</td>
</tr>
<tr>
<td>Axillary</td>
<td>Inferior</td>
<td>Middle</td>
<td>Anterior</td>
<td>C6</td>
</tr>
<tr>
<td>Radial</td>
<td>Inferior</td>
<td>Middle</td>
<td>Posterior</td>
<td>C7</td>
</tr>
<tr>
<td>Median</td>
<td>Inferior</td>
<td>Middle</td>
<td>Superior</td>
<td>C8</td>
</tr>
<tr>
<td>Lower subscapular</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td>T1</td>
</tr>
<tr>
<td>Ulnar</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td>C9</td>
</tr>
<tr>
<td>Medial cutaneous nerves of arm and forearm</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td>T2</td>
</tr>
<tr>
<td>Medial pectoral</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Thoracodorsal</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Upper subscapular</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
<tr>
<td>Superior</td>
<td>Inferior</td>
<td>Superior</td>
<td>Posterior</td>
<td></td>
</tr>
</tbody>
</table>

**Face**

**Figure 10. Skull and facial bones**

1. Lacrimal bone
2. Zygomatic bone
3. Maxilla
4. Mandible
5. Nasal bone
6. Sphenoid bone
7. Temporal bone
8. Parietal bone
9. Occipital bone
10. Frontal bone

**Brachial Plexus Mnemonic**
Rob – Roots
Thomas – Trunks
Drinks – Divisions
Cold – Cords
Beers – Branches
Skin Lesions and Masses

Differential Diagnosis of Skin Lesions/Masses

- for background information and medical management (see Dermatology, D5)
- for biopsy techniques, see Skin Biopsy Types and Techniques, PL7

Surgical Management of Malignant Skin Lesions

- surgical treatment for all malignant skin lesions involve total excision of the primary lesion
- excision margin of lesion depends on the diameter and depth
- for decisions regarding reconstruction using flaps or skin grafts, see Reconstruction, PL11

Precursors of Malignant Lesions

<table>
<thead>
<tr>
<th>Table 1. Precursors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basal Cell Carcinoma</strong></td>
</tr>
<tr>
<td>Nevus sebaceous of Jadassohn</td>
</tr>
<tr>
<td>Bowen's disease</td>
</tr>
<tr>
<td>Paget’s disease</td>
</tr>
<tr>
<td>Erythroplasia</td>
</tr>
</tbody>
</table>

Surgical Margins

<table>
<thead>
<tr>
<th>Table 2. Surgical Margins for Basal Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diameter of Lesion</strong></td>
</tr>
<tr>
<td>≤ 2 cm</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Surgical Margins for Squamous Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diameter or Location of Lesion</strong></td>
</tr>
<tr>
<td>≤ 2 cm*</td>
</tr>
<tr>
<td>&gt; 2 cm</td>
</tr>
<tr>
<td>High risk (facial)</td>
</tr>
<tr>
<td>Low risk (elsewhere)</td>
</tr>
</tbody>
</table>

*For a high risk lesion that is < 2 cm in diameter, use a 6 mm margin
Table 4. Surgical Margins for Malignant Melanoma

<table>
<thead>
<tr>
<th>Depth of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1-4 mm</td>
<td>2 cm</td>
</tr>
<tr>
<td>≥2 mm</td>
<td>Minimum 2 cm</td>
</tr>
</tbody>
</table>

Basic Surgical Techniques

Sutures and Suturing

ANESTHESIA
- debride and irrigate before injecting anesthetic
- toxicity of mixtures (i.e. lidocaine + bupivicaine) is no greater than its individual components

Table 5. Toxic Limit and Duration of Action (1 cc of 1% solution contains 10 mg lidocaine)

<table>
<thead>
<tr>
<th>Suture Material</th>
<th>Toxic Limit</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (Xylocaine®)</td>
<td>5 mg/kg, lasts 45-60 min</td>
<td>45-60 min</td>
</tr>
<tr>
<td>Bupivicaine (Marcaine®)</td>
<td>2 mg/kg, lasts 2-4 h</td>
<td>2-4 h</td>
</tr>
</tbody>
</table>

IRRIGATION AND DEBRIDEMENT
- irrigate copiously with a physiologic solution such as Ringer’s lactate or normal saline to remove surface clots, foreign material, and bacteria
- debride all obviously devitalized tissue, irregular or ragged wounds must be excised to produce sharp wound edges that will assist healing when approximated

SUTURES
- use of a particular suture material is highly dependent on surgeon preference
- suture material divided into absorbable vs. non absorbable and monofilament vs. braided

Table 6. Suture Materials: Absorbable vs. Non-absorbable and Monofilament vs. Multifilament

<table>
<thead>
<tr>
<th>Suture Materials</th>
<th>Uses</th>
<th>Examples</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbable</td>
<td>Deep sutures under short-term tension</td>
<td>Plain gut®, Vicryl®, Polysorb®</td>
<td>loses at least 50% of their strength in 4 wk; eventually absorbed</td>
</tr>
<tr>
<td></td>
<td>Skin closure in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Absorbable</td>
<td>Skin closure (when trauma)</td>
<td>Nylon, polypropylene (Prolene), stainless steel</td>
<td>Lower likelihood of wound dehiscence, more difficult to tie</td>
</tr>
<tr>
<td>Monofilament</td>
<td>Contaminated and infected wounds</td>
<td>Monosof®, Monocryl®, Biosyn®</td>
<td>Slides through tissue with less friction; more memory/stiffness</td>
</tr>
<tr>
<td></td>
<td>(lower likelihood of bacterial trapping in suture material)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifilament</td>
<td>AVOID in contaminated wounds</td>
<td>Vicryl® and Silk</td>
<td>Less memory/stiffness thus easier to work with</td>
</tr>
<tr>
<td></td>
<td>(increased likelihood of bacterial trapping)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BASIC SUTURING TECHNIQUES

Basic Suture Methods
- simple interrupted: can be used in almost all situations
- sub-cuticular: good cosmetic result but weak, used in combination with deep sutures; not used in trauma
- vertical mattress: for areas difficult to evert (e.g. dorsum of the hand)
- horizontal mattress: everting, time saving
- continuous over and over (i.e. “running”, “baseball stitch”): time saving, good for hemostasis

Basic Principles
- minimize tissue trauma: follow curve of needle, insert and exit at 90 degrees to the wound edge, handle wound edges gently (use toothed forceps), use just enough tension to approximate edges (do not stranglelate)
- use the finest needle and suture possible
- ensure good cosmesis

Other Skin Closure Materials
- tapes: may be indicated for superficial wounds and those with opposable edges. Tape cannot be used on actively bleeding wounds. When placed across the incision, will prevent surface marks and can be used primarily or after surface sutures have been removed. Tape burns may occur if there is excessive tension or swelling around the incision
- skin adhesives: e.g. 2-octylcyanoacrylate (e.g. Dermabond®) works well on small areas without much tension or shearing; may cause irreversible tattooing
- staples: steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture)
**Excision**

- plan your incision along relaxed skin tension lines to minimize appearance of scar
- use elliptical incision to prevent “dog ears” (heaped up skin at end of incision) so the length of the ellipse should be 3x the width
- if needed, undermine skin edges to decrease wound tension
- use layered closure including dermal sutures when wound is deeper than superficial (decreases tension)

**Skin Biopsy Types and Techniques**

**SHAVE BIOPSY**
- used for superficial lesions where sampling of the full thickness of the dermis is not necessary
- most suitable lesions for shave biopsies are either elevated above the skin or have pathology confined to the epidermis (e.g. seborrheic or actinic keratoses, skin tags, warts, and superficial basal cell or squamous cell carcinomas)
- rapid, requires little training, and does not require sutures for closure
- will leave a circular scar
- can leave an indented scar
- heals by secondary intent
- should not be used for pigmented lesions – an unsuspected melanoma cannot be properly staged if partially removed

**INCISIONAL BIOPSY**
- can either be a punch biopsy
- or can be an ellipse including the lesion
- gives pathologists a portion of the lesion and the border with normal skin too

**PUNCH BIOPSY**
- involves the removal of a core-shaped piece of tissue, performed with round, disposable knives ranging in diameter from 2-10 mm
- allows sampling of the deep dermis
- can be used for the diagnosis and treatment of small pigmented lesions and atypical moles
- punch biopsy wounds can be closed with suture or left to heal by secondary intention. Punches greater than 3 mm may produce scarring and are best closed with one or two sutures
- has low incidence of infection, bleeding, nonhealing, significant scarring

**EXCISIONAL BIOPSY**
- performed for lesions that require complete removal for diagnostic or therapeutic purposes
- performed for lesions that cannot be adequately punch biopsied due to size, depth, or location
- requires the greatest amount of expertise and time
- always requires sutures for closure

**TECHNIQUE**

**General**
- all biopsies performed in clinic are done using aseptic technique, but are not sterile
- sterile gloves are indicated for biopsies and excisions in all patients

**Preparing the Site**
- common skin antiseptics (betadine, chlorhexidine) can be used to prepare the biopsy site
- chlorhexidine is used in concentrations ranging from 0.5-4%. This higher concentration cannot be used on the face as it could get into the eyes or ears and may burn or cause damage; most chlorhexidine preps also contain alcohol which can be flammable, so allow to dry before the biopsy and certainly before using any cautery
- mark the intended lesion and surgical margins with a surgical marker since they may be temporarily obliterated following injection of the anesthetic
- for all biopsies, a sterile drape technique is indicated. A fenestrated surgical drape is placed around the biopsy site after the area is cleansed and anesthetized

**Anesthesia**
- most commonly used local anesthetic is 1% or 2% lidocaine (with epinephrine)
- small amounts of epinephrine are added to constrict blood vessels, decrease bleeding, prolong anesthesia, and limit lidocaine toxicity. The local with epinephrine can be injected directly into the lesion
- local anesthetics with epinephrine may be used anywhere in the body (including the digits – except if the digits have been significantly injured and could have vascular compromise – e.g. saw injury)
- a field block should be performed for larger lesions by placing a ring of anesthetic around the surgical site, advancing and injecting through a site that has been previously anesthetized
Wounds

Causal Conditions

• laceration: cut or torn tissue
• abrasion: superficial skin layer is removed, variable depth
• contusion: injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact yet injured
• avulsion: tissue/limb forcefully separated from surrounding tissue, either partially or fully; “de-gloving”
• puncture wounds: opening relatively small as compared with depth (e.g. needle)
  ▪ includes bite wounds
• crush injuries: caused by compression
• thermal and chemical wounds

Principles of Wound Healing

• wound: disruption of the normal anatomical relationships of tissue as a result of injury

STAGES OF WOUND HEALING

• growth factors released by tissues play an important role
• scar is mature once it has completed the final stage, usually after 1 yr

FACTORS INFLUENCING WOUND HEALING

Local (reversible/controllable)
• mechanical (local trauma, tension)
• blood supply (ischemia/circulation)
• temperature
• technique and suture materials
• retained foreign body
• infection
• hematoma/seroma (↑ infection rate)
• venous HTN
• peripheral vascular disease

General (often irreversible)
• age
• nutrition (protein, vitamin C, O₂)
• smoking
• chronic illness (e.g. DM, cancer, CVD)
• immunosuppression (steroids, chemo, radiation)
• collagen vascular disease
• tissue irradiation

Myofibroblasts are the cells responsible for wound contraction; they do this at a rate of less than 0.75 mm/d

PHASE

1. Inflammatory Phase (Reactive) (Days 1-6)
  • Limits damage, prevents further injury
  • Debris and organisms cleared via inflammatory response:
    • Neutrophils (24-48 h)
    • Macrophages: critical to wound healing by orchestrating growth factors for collagen production (48-96 h)
    • Lymphocytes: role poorly defined (5-7 d)

2. Proliferative Phase (Regenerative) (Day 4 – Week 3)
  • Fibroblasts attracted and activated by macrophage growth factors
  • Reparative process: re-epithelialization, matrix synthesis, angiogenesis (relieves ischemia)
  • Tensile strength begins to increase at 4-5 d

3. Remodeling Phase (Maturation) (Week 3 – 1 year)
  • Increasing collagen organization and stronger crosslinks
  • Type I collagen replaces Type III until normal 4:1 ratio achieved
  • Peak tensile strength at 60 d – 80% of preinjury strength

PROCESS

1. Hemostasis – vasoconstriction + platelet plug
2. Chemotaxis – migration of macrophages and PMN

1. Collagen synthesis (mainly type III)
2. Angiogenesis
3. Epithelialization

1. Contraction
2. Scarring
3. Remodeling of scar

Figure 14. Stages of wound healing
ABNORMAL HEALING

Hypertrophic Scar
- scar remains roughly within boundaries of original injury
- red, raised, widened, frequently pruritic
- usually caused by excess tension on a wound or delayed closure (as in burn wounds)
- common sites: back, shoulder, sternum, angle of mandible
- treatment: pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur), fractional carbon dioxide ablative laser
- typically improves with time

Keloid Scar
- scar extends beyond boundaries of original injury
- frequently pruritic, often painful; collagen in whorls rather than bundles
- common sites: sternum, deltoid, earlobe; more common in darker skinned people
- treatment: pressure garments, silicone gel sheeting, corticosteroid injection, radiation therapy ± surgical excision as a last resort
- unlike hypertrophic scar, this is due to a derrangement in normal wound healing caused by over-active fibroblasts due to excessive transforming growth factor-beta expression

Chronic Wound
- fails to heal primarily within 4-6 wk
- common chronic wounds include diabetic, pressure and venous stasis ulcers
- treatment: may heal with meticulous wound care; may also require surgical intervention
- Marjolin’s ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation → consider biopsy of chronic wound

WOUND CLOSURE

Primary (1o) Closure (First Intention)
- definition: wound closure by direct approximation of edges within hours of wound creation (i.e. with sutures, staples, skin graft, etc.)
- indication: recent (<6 h, longer with facial wounds), clean wounds
- contraindications: animal/human bites (except on face), crush injuries, infection, long time lapse since injury (>6-8 h), retained foreign body

Secondary (2o) Closure/Spontaneous Healing (Second Intention)
- definition: wound left open to heal spontaneously (epithelialization 1 mm/d from wound margins in concentric pattern), contraction (myofibroblasts) and granulation – maintained in inflammatory phase until wound closed; requires dressing changes; inferior cosmetic result
- indication: when 1° closure not possible or indicated (see Primary Closure)

Tertiary (3o) Closure/Delayed Primary Closure (Third Intention)
- definition: intentionally interrupt healing process (e.g. with packing), then wound can be closed at 4-10 d post-injury after granulation tissue has formed and there is <10^6 bacteria/gram of tissue
- indication: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization, closure of fasciotomy wounds
- prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

Contaminated and Infected Wounds

Definitions
- contamination: the presence of non-replicating microorganisms within a wound
- colonization: the presence of replicating microorganisms within a wound
- infection: greater than 10^6 microorganisms in a wound without intact epithelium, a wound may also be infected with small amounts of a very virulent organism (e.g. GBS)

Management of Acute Contaminated Wound (<24 h)
- cleanse and irrigate open wound with physiologic solution (NS or RL)
- evaluate for injury to underlying structures (vessels, nerve, tendon and bone)
- control active bleeding
- debridement: removal of foreign material, devitalized tissue, old blood
- surgical debridement: blade and irrigation if indicated
- systemic antibiotics are commonly indicated for obvious infection, wound older than 8 h, severely contaminated, human/animal bites, immunocompromised, involvement of deeper structures (e.g. joints, fractures)
- ± tetanus toxoid 0.5 mL IM ± tetanus immunoglobulin 250 U deep IM (see Table 7 and Table 8)
• ± post-exposure treatment of
  - hepatitis B, HIV, hepatitis C (if titres confirmed at 6 mo)
• re-evaluate in 24-48 h for signs of deep infection
  - open infected portion of wound by removing sutures if evidence of infection (i.e. erythema, warmth, pain, discharge)

<table>
<thead>
<tr>
<th>Table 7. Risks for Tetanus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Characteristics</td>
</tr>
<tr>
<td>Time since injury</td>
</tr>
<tr>
<td>Depth of injury</td>
</tr>
<tr>
<td>Mechanism of Injury</td>
</tr>
<tr>
<td>Devitalized tissue</td>
</tr>
<tr>
<td>Contamination (e.g. soil, dirt, saliva, grass)</td>
</tr>
<tr>
<td>Retained foreign body</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 8. Tetanus Immunization Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of Tetanus Immunization</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Uncertain or &lt;3 doses of immunization</td>
</tr>
<tr>
<td>3 doses received in immunization series</td>
</tr>
</tbody>
</table>

* 0.5 mL of combined tetanus and diphtheria toxoids = acellular pertussis
** Tetanus immune globulin, 250 U given at a separate site from Td/Tdap
§ Yes, if >5 yr since last booster
¶ Yes, if immunocompromised

Management of Contaminated Wounds (>24 h, including Ulcers)
• irrigation and debridement
  ▪ traumatic tattooing can occur if foreign materials left in wound
• systemic antibiotics indicated if there is concern of infection (e.g. redness, swelling, pain, clinically unwell)
• topical antimicrobials: beneficial for minor wounds, but no additional benefit for wounds requiring systemic antibiotics. May aid in healing of chronic wounds
• closure: final closure via secondary intention (most common), delayed wound closure (3º closure), skin graft or flap; successful closure depends on bacterial count of ≤10⁵/cm³ prior to closure and frequent dressing changes

BITES
• see Emergency Medicine, ER46

Dog and Cat Bites
• pathogens: Pasteurella multocida, S. aureus, S. viridans
• investigations: same as for human bites
• treatment: Clavulin® (500 mg PO q8h started immediately – amoxicillin + clavulanic acid)
  ▪ consider rabies prophylaxis if animal has symptoms of rabies or unknown animal
  ▪ ± rabies lq (20 IU/kg around wound, or IM) and 1 of the 3 types of rabies vaccines (1.0 mL IM in deltoid, repeat on days 3, 7, 14, 28)
  ▪ aggressive irrigation with debridement
  ▪ healing by secondary intention is mainstay of treatment
  ▪ only consider primary closure for bite wounds on the face; otherwise primary closure is contraindicated
  ▪ contact Public Health if animal status unknown

Human Bites
• pathogens: Staphylococcus > α-hemolytic Streptococcus > Eikenella corrodens > Bacteroides
• mechanism: most commonly over dorsum of MCP from a punch in mouth; “fight-bite”
• serious, as mouth has 10⁹ microorganisms/mL, which get trapped in joint space when fist unclenches and overlying skin forms an air-tight covering ideal for anaerobic growth – can lead to septic arthritis
• investigations:
  ▪ radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  ▪ culture for aerobic and anaerobic organisms, Gram stain
• treatment
  ▪ urgent surgical exploration of joint, drainage and debridement of infected tissue
  ▪ wound must be copiously irrigated
  ▪ Clavulin® 500 mg PO q8h, clindamycin 300 mg PO q6h + ciprofloxacin 500 mg PO q12h
  (if allergic to penicillin) + secondary closure
  ▪ splint

Dressings

• dressing selection depends on the wound characteristics
  ▪ as the wound progresses through healing it will require different types of dressings, therefore, routine inspection is recommended
  ▪ principles of dressings
    • moist vs. dry wounds
      – purpose of dressings should be to keep wound appropriately moist (i.e. moistening dry wounds or removing excess exudate/blood from wet wounds)
    • clean vs. infected wounds
      – clean wounds can be dressed with petroleum based gauze, which is non-adhering to epithelializing tissue; requires secondary dressing
      – infected wounds can be dressed with iodine gauze, silver-containing, or antimicrobial dressings
    • wide-based vs. cavitary/tunneling wounds
      – cavitary or tunnelling wounds (i.e. through a fascial layer) can be packed with saline-soaked (non-infected), betadine or chlorpactin-soaked (infected) ribbon gauze, or other easily retrievable one-piece moisture providing dressing

Table 9. Recommended Dressings for Wound Type

<table>
<thead>
<tr>
<th>Wound Depth</th>
<th>Exudate Level</th>
<th>Dressing Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>Lightly exuding</td>
<td>Films (Opsite®), hydrogels (Intrasite®, Nu-gel®, Duoderm®)</td>
</tr>
<tr>
<td></td>
<td>Any exudate level</td>
<td>Contact layers</td>
</tr>
<tr>
<td>Superficial to Deep</td>
<td>Light to moderately exuding wounds</td>
<td>Amorphous gels, hydrogels, hydrocolloids (Duoderm®, Tegaderm®), collagen, hypertonic saline gauze (Mesalt®)</td>
</tr>
<tr>
<td></td>
<td>Moderately to heavily exuding wounds</td>
<td>Foams (Mepilex®, Allevyn®), alginates (Sorbsan®, Kaltostat®), hypertonic saline gauze, hydrofiber (Aquacel®)</td>
</tr>
</tbody>
</table>

Table adapted from Grabb & Smith's Plastic Surgery, 6th ed. Chapter 3, Table 3.3

Reconstruction

SKIN GRAFTS

Definition

• skin that is harvested from a donor site and transferred to the recipient site and that does not carry its own blood supply. Survival requires diffusion of nutrients during the first 24-48 h (imbibition) followed by blood vessel connection between the donor site and graft (inosculation). They are classified according to the depth of dermis they contain: full thickness (entire epidermis + dermis) vs. split-thickness (epidermis + partial dermis)

Donor Site Selection

• must consider size, hair pattern, texture, thickness of skin, and color (facial grafts best if taken from "blush zones" above clavicle e.g. pre/post auricular or neck)
• partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)

Partial Thickness Skin Graft Survival

• 3 phases of skin graft "take"
  1. plasmatic imbibition: diffusion of nutrition from recipient site (first 48 h)
  2. inosculation: vessels in graft connect with those in recipient bed (day 2-3)
  3. neovascular ingrowth: graft revascularized (day 3-5)
• requirements for survival
  ▪ bed: well-vascularized (unsuitable: bone, tendon, heavily irradiated, infected wounds, etc.)
  ▪ contact between graft and recipient bed: fully immobile (decreased shearing and hematoma formation)
  ▪ staples, sutures, splinting, and appropriate dressings (pressure) are used to prevent movement of graft and hematoma or seroma formation
  ▪ site: low bacterial count (<10^5/cm^2, to prevent infection)
Classification of Skin Grafts

1. by species
   - autograft: from same individual
   - allograft (homograft): from same species, different individual
   - xenograft (heterograft): from different species (e.g. porcine)

2. by thickness

<table>
<thead>
<tr>
<th>Table 10. Skin Grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Donor Site</strong></td>
</tr>
<tr>
<td><strong>Healing of Donor Site</strong></td>
</tr>
<tr>
<td><strong>Re-harvesting</strong></td>
</tr>
<tr>
<td><strong>Graft Take</strong></td>
</tr>
<tr>
<td><strong>Contraction</strong></td>
</tr>
<tr>
<td><strong>Aesthetic</strong></td>
</tr>
<tr>
<td><strong>Comments</strong></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
</tr>
<tr>
<td><strong>Uses</strong></td>
</tr>
</tbody>
</table>

- mesh graft
  - advantages
    - prevents accumulation of fluids (e.g. hematoma, seroma)
    - covers a larger area
  - disadvantages
    - poor cosmesis (“reptilian” appearance)
    - has significant contractures

- common reasons for graft loss: hematoma/seroma, infection, mechanical force (e.g. shearing, pressure)

**OTHER GRAFTS**

<table>
<thead>
<tr>
<th>Table 11. Various Tissue Grafts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Graft Type</strong></td>
</tr>
<tr>
<td><strong>Bone</strong></td>
</tr>
<tr>
<td><strong>Cartilage</strong></td>
</tr>
<tr>
<td><strong>Tendon</strong></td>
</tr>
<tr>
<td><strong>Nerve</strong></td>
</tr>
<tr>
<td><strong>Vessel</strong></td>
</tr>
<tr>
<td><strong>Dermis</strong></td>
</tr>
<tr>
<td><strong>Fat</strong></td>
</tr>
</tbody>
</table>

**FLAPS**

- **definition:** tissue transferred from one site to another with a known blood supply (random, pediced or named); not dependent on neovascularization, unlike a graft
- **may consist of:** skin, subcutaneous tissue, fascia, muscle, bone, other tissue (e.g. omentum)
- **classification:** based on blood supply to skin (random, axial) and anatomic location (local, regional, distant)
- **indications for flaps**
  - reconstruction: replaces tissue loss due to trauma or surgery
  - provides skin and temporary soft tissue coverage through which surgery can be carried out later
  - improves blood supply to poorly vascularized bed (e.g. bone)
- **complications:** flap loss due to hematoma, seroma, infection, poor flap design, extrinsic compression (dressing too tight) or vascular failure/thrombosis, fat necrosis (in free flaps)
Random Pattern Flaps
- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply (typically 2:1)
- flap choice is often a combination of available tissue, location of reconstruction site with respect to donor site, and surgeon preference
- types
  - rotation: cover wounds of various sizes; common use: sacral pressure sores
  - transposition: smaller in size compared to rotation flaps and advancement flaps; commonly used on certain areas of the face using adjacent areas of excess skin laxity
  - Z-plasty: used to reorient a scar, lengthen the line of a scar or to break up a scar
  - advancement flaps (V-Y, Y-V)
    - single/bipedicle V-Y flaps: wounds with lax surrounding tissue; the pedicle is the deep tissue underlying the flap

Axial Pattern Flaps (Arterialized)
- flap contains a well defined artery and vein
- allows greater length:width ratio (5-6:1)
- types
  - peninsular flap: skin and vessel intact in pedicle
  - island flap: vessel intact, pedicle is better defined
  - free flap: vascular supply anastomosed at recipient site by microsurgical techniques
- can be sub-classified according to tissue content of flap:
  - e.g. musculocutaneous/myocutaneous (e.g. transverse rectus abdominal myocutaneous) vs. fasciocutaneous

Free Flaps
- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and veins to a flap and performing a microscopic anastomosis between these and the vessels in the recipient wound
- survival rates >95%
- types: muscle and skin (common), bone, jejunum, omentum
  - e.g. radial forearm, scapular, latissimus dorsi

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Arterial Insufficiency</th>
<th>Venous Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color</td>
<td>Pink</td>
<td>Pale</td>
<td>Purple or blue</td>
</tr>
<tr>
<td>Temperature</td>
<td>Warm</td>
<td>Cool</td>
<td>Warm or cool</td>
</tr>
<tr>
<td>Arterial Pulse (Doppler)</td>
<td>+</td>
<td>±</td>
<td>±</td>
</tr>
<tr>
<td>Turgor</td>
<td>Soft, but with tissue turgor</td>
<td>Decreased</td>
<td>Increased (i.e. tense)</td>
</tr>
</tbody>
</table>
# Soft Tissue Infections

## Table 13. Classification of Soft Tissue Infections by Depth

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erysipelas</td>
<td>Superficial with subcutaneous tissue involvement</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Full thickness with subcutaneous tissue involvement</td>
</tr>
<tr>
<td>Fasciitis</td>
<td>Fascia</td>
</tr>
<tr>
<td>Myositis</td>
<td>Muscle</td>
</tr>
</tbody>
</table>

## Erysipelas

**Definition**
- acute skin infection that is more superficial than cellulitis

**Etiology**
- typically caused by Group A β-hemolytic Streptococcus

**Clinical Features**
- intense erythema, induration, and **sharply demarcated borders** (differentiates it from other skin infections)

**Treatment**
- penicillin or first generation cephalosporin (e.g. cefazolin or cephalexin)

## Cellulitis

**Definition**
- non-suppurative infection of skin and subcutaneous tissues

**Etiology**
- skin flora most common organisms: *S. aureus*, β-hemolytic *Streptococcus*
- immunocompromised: Gram-negative rods and fungi

**Clinical Features**
- source of infection
  - trauma, recent surgery
  - foreign bodies (IV, orthopaedic pins)
  - systemic symptoms (fever, chills, malaise)
- pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (visible red streaking in skin proximal to area of cellulitis)

**Investigations**
- CBC, blood cultures
- culture and Gram stain wound/aspirate from wound if open wound
- plain radiographs if suspect foreign body or abscess or to rule out gas (if worried about a deeper infection, e.g. fasciitis) or rule out bone invasion (osteomyelitis)

**Treatment**
- antibiotics: first line – cephalaxin 500 mg PO q6h or cloxacillin 500 mg PO q6h x 7 d;
  - if complicated (e.g. lymphangitis, DM) consider IV cefazolin 1-2 g q8h penicillin
- outline area of erythema to monitor success of treatment
- immobilize and splint (hands)

## Necrotizing Fasciitis

**Definition**
- rapidly spreading, very painful infection of the deep fascia with necrosis of tissues
- some bacteria create gas that can be felt as crepitus and be seen on x-rays
- infection spreads rapidly along deep fascial plane and is **limb and life threatening**

**Etiology**
- Type I: polymicrobial (less aggressive)
- Type II: monomicrobial, usually β-hemolytic *Streptococcus*
Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema, edema, tenderness, ± crepitus (subcutaneous gas from anaerobes) ± fever
- infection spreads very rapidly
- hypotension and hyperglycemia are common findings
- patients may look deceptively well at first, but may rapidly become very sick/toxic
- late findings
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of bullae
  - cutaneous gangrene, subcutaneous emphysema

Investigations
- a clinical diagnosis
- CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, gas collection, myonecrosis and possible source of infection)
- severely elevated CK: usually means myonecrosis (late sign)
- hemostat easily passed along fascial plane; fascial biopsy to rule out in equivocal situations

Treatment
- vigorous resuscitation (ABCs)
- urgent surgical debridement: remove all necrotic tissue, copious irrigation
- IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4h and clindamycin 900 mg IV q6h until final cultures available; clindamycin targets the toxin produced
- possible role for IVIg (especially in Group A strep, adjuvant treatment on a case by case basis)
- urgent consultation with infectious disease specialist is recommended

Ulcers

Lower Limb Ulcers

Traumatic Ulcers (Acute)
- failure of lesions to heal, usually due to compromised blood supply and unstable scar
- usually over bony prominence ± edema ± pigmentation changes ± pain
- treatment: debridement of ulcer and compromised tissue, left to heal via secondary intention with dressings, may need reconstruction with local or distant flap in select cases, vascular status of limb must be assessed clinically and via vascular studies (i.e. sonographically)

Non-Traumatic Ulcers (Chronic)

Table 14. Venous vs. Arterial vs. Diabetic Ulcers

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venous (70% of vascular ulcers)</th>
<th>Arterial</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Valvular incompetence</td>
<td>2nd to small and/or large vessel disease (be aware of risk factors)</td>
<td>Peripheral neuropathy: decreased sensation</td>
</tr>
<tr>
<td></td>
<td>Venous HTN</td>
<td></td>
<td>Atherosclerosis: decreased regional blood flow</td>
</tr>
<tr>
<td>History</td>
<td>Dependent edema, trauma</td>
<td>Arteriosclerosis, claudication</td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Rapid onset ± thrombophlebitis, varicosities</td>
<td>Usually &gt;45 yr Slow progression</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td>Common Distribution</td>
<td>Medial malleolus,</td>
<td>Distal locations</td>
<td>Pressure point distribution</td>
</tr>
<tr>
<td></td>
<td>(&quot;Gaiter&quot; locations)</td>
<td>(e.g. toes)</td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td>Yellow exudates, Granulation tissue</td>
<td>Pale/white, necrotic base ± dry eschar covering</td>
<td>Necrotic base</td>
</tr>
<tr>
<td></td>
<td>Varicose veins, Brown discoloration of surrounding skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound Margins</td>
<td>Irregular</td>
<td>Even (&quot;punched out&quot;)</td>
<td>Irregular or &quot;punched out&quot; or deep</td>
</tr>
<tr>
<td>Depth</td>
<td>Superficial</td>
<td>Superficial/deep</td>
<td></td>
</tr>
<tr>
<td>Surrounding Skin</td>
<td>Venous stasis discoloration (brown)</td>
<td>Thin shiny dry, hairless, cool</td>
<td>Thin dry skin ± hyperkeratotic border</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitive/sclerotic</td>
</tr>
<tr>
<td>Pulses</td>
<td>Normal distal pulses</td>
<td>Decreased or no distal pulses</td>
<td>Decreased pulses likely</td>
</tr>
<tr>
<td>Vascular Exam</td>
<td>ABI &gt; 0.9</td>
<td>ABI &lt; 0.9</td>
<td>ABI is inaccurately high</td>
</tr>
<tr>
<td></td>
<td>Doppler, abnormal venous system</td>
<td>Rollover on elevation, rubor on dependency</td>
<td>Usually associated with arterial disease</td>
</tr>
</tbody>
</table>

ABI in diabetics can be falsely normal due to incompressible arteries secondary to plaques/calcification

All chronic ulcers require vascular studies, and a vascular consult, to assess for venous insufficiency, to rule in/out arterial pathology and to find out the potential role of vascular surgical management
Table 14. Venous vs. Arterial vs. Diabetic Ulcers (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venous (70% vascular ulcers)</th>
<th>Arterial</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Moderately painful</td>
<td>Extremely painful</td>
<td>Painless</td>
</tr>
<tr>
<td></td>
<td>Increased with leg dependency,</td>
<td>Decreased with dependency,</td>
<td>No claudication or rest pain</td>
</tr>
<tr>
<td></td>
<td>decreased with elevation</td>
<td>increased with leg elevation and</td>
<td>Associated paresthesia,</td>
</tr>
<tr>
<td></td>
<td>No rest pain</td>
<td>exercise (claudication)</td>
<td>anesthesia</td>
</tr>
<tr>
<td></td>
<td>Rest pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Leg elevation, rest</td>
<td>Rest, no elevation, no compression</td>
<td>Control DM</td>
</tr>
<tr>
<td></td>
<td>Compression at 30 mmHg</td>
<td>Moist wound dressing ± topical</td>
<td>Careful wound care</td>
</tr>
<tr>
<td></td>
<td>(stockings or elastic bandages)</td>
<td>and/or systemic antibiotics</td>
<td>Foot care</td>
</tr>
<tr>
<td></td>
<td>Moist wound dressings ±</td>
<td>Modify risk factors (smoking, diet,</td>
<td>Orthotics</td>
</tr>
<tr>
<td></td>
<td>topical, systemic antibiotics</td>
<td>exercise, etc.)</td>
<td>Early intervention for infections</td>
</tr>
<tr>
<td></td>
<td>± skin grafts</td>
<td>Vascular surgical consultation</td>
<td>(topical and/or systemic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(angioplasty or bypass)</td>
<td>antibiotics)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treat underlying conditions (DM,</td>
<td>Vascular surgical consultation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>proximal arterial occlusion, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

Pressure Ulcers

Common Sites
- over bony prominences; 95% on lower body

Stages of Development
1. hyperemia: disappears 1 h after pressure removed
2. ischemia: follows 2–6 h of pressure
3. necrosis: follows >6 h of pressure
4. ulcer: necrotic area breaks down – N.B. skin is like tip of an iceberg

Classification (National Pressure Ulcer Advisory Panel 2007)
- Stage I: nonblanchable erythema present >1 h after pressure relief, skin intact
- Stage II: partial-thickness skin loss
- Stage III: full-thickness skin loss into subcutaneous tissue, but not through fascia
- Stage IV: through fascia into muscle, bone, tendon, or joint
  - if an eschar is present, must fully debride before staging possible

Prevention
- good nursing care (clean dry skin, frequent repositioning), special beds or mattress (Kin Air*), proper nutrition, activity, early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, etc.)

Treatment
- depends on individual patient and condition
- treat underlying medical issues including nutrition
- continue with preventative measures (pressure relief)
- wound debridement, moisture retentive or antimicrobial dressing, regular reassessment
- topical antimicrobials at treating physician’s discretion, systemic antibiotics for infections
- resect osteomyelitis and treat with 6 wk of antibiotics before final flap coverage
- assess for possible reconstruction after infection eradicated and clean wound bed (<10^5 colony-forming unit)

Complications
- cellulitis, osteomyelitis, sepsis, gangrene

Burns

Burn Injuries

Causal Conditions
- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

Most Common Etiology
- children: scald burns
- adults: flame burns
Table 15. Skin Function and Burn Injury

<table>
<thead>
<tr>
<th>Skin Function</th>
<th>Consequence of Burn Injury</th>
<th>Intervention Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoregulation</td>
<td>Prone to lose body heat</td>
<td>Must keep patient covered and warm</td>
</tr>
<tr>
<td>Control of fluid loss</td>
<td>Loss of large amounts of water and protein from the skin and other body tissues</td>
<td>Adequate fluid resuscitation is imperative</td>
</tr>
<tr>
<td>Mechanical barrier to bacterial invasion and immunological organ</td>
<td>High risk of infection</td>
<td>Antibiotic ointments (systemic if signs of specific infection present) Tetanus prophylaxis if necessary</td>
</tr>
</tbody>
</table>

**Pathophysiology of Burn Wounds**

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent
- **zone of hyperemia**: vasodilation from inflammation; entirely viable, cells recover within 7 d; contributes to systemic consequences seen with major burns
- **zone of stasis (edema)**: decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24-48 h without proper treatment
  - factors favoring cell survival: moist, aseptic environment, rich blood supply
  - zone where appropriate early intervention has most profound effect in minimizing injury
- **zone of coagulation (ischemia)**: no blood flow to tissue → irreversible cell damage → cellular death/necrosis

**Diagnosis and Prognosis**

- burn size
  - % of TBSA burned: rule of 9s for 2° and 3° burns only (children <10 yr old use Lund-Browder chart)
  - for patchy burns, surface area covered by patient’s palm (fingers closed) represents approximately 1% of TBSA
- age: more complications if <3 or >60 yr old
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see Table 16)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see *Indications for Transfer to Burn Center*, PL18)
- inhalation injury: can severely compromise respiratory system due to sloughing of the epithelium that blocks gas exchange at the alveolus; also significant swelling of the intraoral and laryngeal mucosa from the thermal injury as well as during massive resuscitation.
- associated injuries (e.g. fractures)
- comorbid factors (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure) can exacerbate extent of injury

**Prognosis best determined by:**

- burn size (TBSA)
- age of patient
- presence/absence of inhalational injury

Figure 18. Zones of thermal injury

Figure 19. Rule of 9s for TBSA
Table 16. Burn Depth (1st, 2nd, 3rd degree)

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Traditional Nomenclature</th>
<th>Depth</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema/Superficial</td>
<td>First degree</td>
<td>Epidermis</td>
<td>Painful, sensation intact, erythema, blanchable</td>
</tr>
<tr>
<td>Superficial-Partial Thickness</td>
<td>Second degree</td>
<td>Into superficial dermis</td>
<td>Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present</td>
</tr>
<tr>
<td>Deep-Partial Thickness</td>
<td>Second degree</td>
<td>Into deep (reticular) dermis</td>
<td>Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn</td>
</tr>
<tr>
<td>Full Thickness</td>
<td>Third degree</td>
<td>Through epidermis and dermis</td>
<td>Insensate (nerve endings destroyed), hard leathery eschar that is black, gray, white, or cherry red in color, hairs do not stay attached, may see thrombosed veins</td>
</tr>
</tbody>
</table>

Indications for Transfer to Burn Center

American Burn Association Criteria
- patients with partial or full-thickness burns that involve the hands, feet, genitalia, face, eyes, ears and/or major joints or perineum
- partial thickness burns ≥20% TBSA in patients aged 10-50 yr old
- partial thickness burns ≥10% TBSA in children aged ≤10 or adults aged ≥50 yr old
- full thickness burns ≥5% TBSA in patients of all ages
- electrical burns, including lightening (internal injury underestimated by TBSA)
- chemical burns
- inhalation injury (high risk of mortality and may lead to respiratory distress)
- burn injuries in patients with medical comorbidities, could complicate management and recovery
- any patient with simultaneous trauma plus burns should be stabilized for trauma first, then triaged appropriately to burn center
- any patients with burn injury and who will require special emotional, social, and rehabilitation intervention
- children with burns in a hospital not equipped with pediatric care specialists
Acute Care of Burn Patients

- adhere to ATLS protocol
- resuscitation using Parkland formula to restore plasma volume and cardiac output and should only be used in burns 30% or greater TBSA
  - 4 cc RL/kg/% TBSA over first 24 h (1/2 within first 8 h of sustaining burn, 1/2 in next 16 h); if resuscitation is greater than 6cc/kg/TBSA, reevaluate as this can create significant complications (compartment syndrome of extremities as well as abdomen which can impair ventilation); reasonable to supplement colloid in setting of excessive resuscitation
- extra fluid administration required if
  - burn >80% TBSA
  - 4° burns
  - associated traumatic injury
  - electrical burn
  - inhalation injury
  - delayed start of resuscitation
  - pediatric burns
- monitor resuscitation
  - urine output is best measure: maintain at >0.5 cc/kg/h (adults) and 1.0 cc/kg/h (children <12 yr)
  - maintain a clear sensorium, HR <120/min, MAP >70 mmHg
  - urine output will often lag early in the resuscitation
  - trend other signs of resuscitation, such as lactate, base deficit, CVP, mixed or central venous O₂
- burn specific care
  - relieve respiratory distress: intubation and/or escharotomy (see sidebar)
  - prevent and/or treat burn shock: at least 2 large bore IVs in non-burned area; place early central line and a-line if large burn identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
  - determine TBSA affected first, since depth is difficult to determine initially (easier to determine after 24 h)
- tetanus prophylaxis if needed
  - all patients with burns >10% TBSA, or deeper than superficial partial thickness, need 0.5 cc tetanus toxoid
  - also give 250 U of tetanus Ig if prior immunization is absent/unclear, or the last booster >10 yr ago
- baseline laboratory studies (Hb, U/A, BUN, CXR, electrolytes, ECG, cross-match, ABG, carboxyhemoglobin)
- cleanse, debride, and treat the burn injury (antimicrobial dressings)
- early excision and grafting important for outcome

Respiratory Problems

- 3 major causes
  - burn eschar encircling chest
  - distress may be apparent immediately
  - perform escharotomy to relieve constriction
- CO poisoning
  - may present immediately or later
  - treat with 100% O₂ (decreases half-life of carboxyhemoglobin from 210 to 59 min) until carboxyHb <10%; can use hyperbaric chamber for very high levels if patient is otherwise stable
  - smoke inhalation leading to pulmonary injury
  - chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
  - risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
  - watch for secondary bronchopneumonia (3-25 d) leading to progressive pulmonary insufficiency
  - intubate patient with any signs of inhalation injuries

Burn Shock Resuscitation (Parkland Formula)

<table>
<thead>
<tr>
<th>Hour</th>
<th>Fluid Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24</td>
<td>4 cc RL/kg/% TBSA with 1/2 of total in first 8 h from time of injury and 1/2 of total in next 16 h from time of injury</td>
</tr>
<tr>
<td>24-30</td>
<td>0.35-0.5 cc plasma/kg/%TBSA, or decrease fluids by 1/3 from first 24 h assuming urine output remains stable</td>
</tr>
<tr>
<td>&gt;30</td>
<td>DSW at rate to maintain normal serum sodium</td>
</tr>
</tbody>
</table>

*Do not forget to add maintenance fluid to resuscitation
Table 18. Burn Wound Healing

<table>
<thead>
<tr>
<th>Depth</th>
<th>Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree</td>
<td>No scarring; complete healing</td>
</tr>
<tr>
<td>Second degree</td>
<td>Spontaneously re-epithelialize in 7 to 14 d from retained epidermal</td>
</tr>
<tr>
<td>(Superficial partial)</td>
<td>structures ± residual skin discoloration</td>
</tr>
<tr>
<td></td>
<td>Hypertrophic scarring uncommon; grafting rarely required</td>
</tr>
<tr>
<td>Deep second degree</td>
<td>Re-epithelialize in 14-35 d from retained epidermal structures</td>
</tr>
<tr>
<td>(Deep partial)</td>
<td>Hypertrophic scarring frequent</td>
</tr>
<tr>
<td></td>
<td>Grafting recommended to expedite healing</td>
</tr>
<tr>
<td>Third degree (Full</td>
<td>Re-epithelialize from the wound edge</td>
</tr>
<tr>
<td>thickness)</td>
<td>Grafting/flap necessary to replace dermal integrity, limit hypertrophic scarring</td>
</tr>
<tr>
<td>Fourth degree</td>
<td>Often results in amputations If not requiring amputation, needs flap for coverage after debridement (do not re-epithelialize – cannot graft)</td>
</tr>
</tbody>
</table>

Treatment

- 3 stages
  1. assessment: depth determined
  2. management: specific to depth of burn and associated injuries
  3. rehabilitation

- first degree
  - treatment aimed at comfort
    - topical creams (pain control, keep skin moist) ± aloe
    - oral NSAIDs (pain control)

- superficial second degree
  - daily dressing changes with topical antibiotics, polysporin, may use a temporary biological or synthetic covering to close the wound

- deep second degree and third degree
  - prevent infection and sepsis (significant cause of death in burn patients)
    - most common organisms: *S. aureus, P. aeruginosa* and *C. albicans*
      - day 1-3 (rare): Gram-positive
      - day 3-5: Gram-negative (*Proteus, Klebsiella*)
    - topical antimicrobials: prevent bacterial infection (from skin flora, gut flora or caregiver) and secondary sepsis
  - remove dead tissue
    - surgically debride necrotic tissue, excise to viable (bleeding) tissue

Table 19. Topical Antibiotic Therapy for Burns

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pain with Application</th>
<th>Penetration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver nitrate (0.5% solution)</td>
<td>None</td>
<td>Minimal</td>
<td>Stains (black), leaches sodium and magnesium from wounds</td>
</tr>
<tr>
<td>Nanocrystalline silver-coated dressing (Acticoat®)</td>
<td>None or transient</td>
<td>Medium, does not penetrate eschar; preferred over silver sulfadiazine and silver nitrate</td>
<td>May stain, producing a pseudoeschar or facial discoloration (argyria-like symptoms); raised liver enzymes</td>
</tr>
<tr>
<td>Silver sulfadiazine (cream) (Silvadene®)</td>
<td>Minimal</td>
<td>Medium, does not penetrate eschar</td>
<td>Slowed healing, leukopenia, mild inhibition of epithelialization</td>
</tr>
<tr>
<td>Mafenide acetate (solution/cream) (Sulfamylon®)</td>
<td>Moderate</td>
<td>Well, penetrates eschar</td>
<td>Mild inhibition of epithelialization, may cause metabolic acidosis with wide application</td>
</tr>
</tbody>
</table>

- early excision and grafting is the mainstay of treatment
- initial dressing should decrease bacterial proliferation
- indication for skin graft: deep 2° or 3° burn that is > size of a quarter
- prevention of wound contractures: pressure dressings, joint splints, early physiotherapy

Other Considerations in Burn Management

![Figure 21. Systemic effects of severe burns](image-url)
• nutrition
  ▪ hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
  ▪ calories, vitamin C, vitamin A, Ca²⁺, Zn²⁺, Fe²⁺
• immunosuppression and sepsis
  ▪ must keep bacterial count <10⁵ bacteria/g of tissue (blood culture may not be positive)
  ▪ signs of sepsis: sudden onset of hyper/hypothermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 h post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
  ▪ oxandrolone has been shown to help with burn induced hypermetabolism in burns over 30% TBSA; continue for up to 6 mo
• GI bleed may occur with burns >40% TBSA (usually subclinical)
  ▪ treatment: tube feeding or NPO, antacids, H₂ blockers (preventative)
• renal failure secondary to under resuscitation, drugs, myoglobin, etc.
• progressive pulmonary insufficiency
  ▪ can occur aft: smoke inhalation, pneumonia, cardiac decompensation, sepsis
• wound contracture and hypertrophic scarring
  ▪ largely preventable with timely wound closure, splinting, pressure garments and physiotherapy; can be treated with fractional ablative CO₂ laser

Special Considerations

CHEMICAL BURNS
• major categories: acid burns, alkaline burns, phosphorous burns, chemical injection injuries
• common agents: cement, hydrofluoric acid, phenol, tar
• mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
  ▪ acids → coagulation necrosis
  ▪ alkalines → saponification followed by liquefactive necrosis
• severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
• burns are deeper than they initially appear and may progress with time

Treatment (General)
• ABCs, monitoring
• remove contaminated clothing and brush off any dry powders before irrigation
• irrigation with water for 1-2 h under low pressure (contraindicated in heavy metal burns, such as sodium, potassium, magnesium, and lithium; in these cases soak in mineral oil instead)
• inspect eyes, if affected: wash with saline and refer to ophthalmology
• inspect nails, hair and webspaces
• correct metabolic abnormalities and tetanus prophylaxis if necessary
• local wound care 12 h after initial dilution (debridement)
• wound closure same as for thermal burn
• beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

Special Burns and Treatments

| Acid Burn | Water irrigation, followed by dilute solution of sodium bicarbonate |
| Hydrofluoric Acid | Water irrigation; clip fingernails to avoid acid trapping; topical calcium gel ± subcutaneous injection of calcium gluconate ± 10% calcium gluconate IV depending on amount of exposure and pain |
| Sulfuric Acid | Treat with soap/lime prior to irrigation, as direct water exposure produces extreme heat |
| Tar | Remove with repeated application of petroleum-based antibiotic ointments (e.g. Polysporin®) |

ELECTRICAL BURNS
• depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
• often presents as small punctate burns on skin with extensive deep tissue damage which requires debridement
• electrical burns require ongoing monitoring as latent injuries can occur
• watch for system specific damages and abnormalities
  ▪ abdominal: intraperitoneal damage
  ▪ bone: fractures and dislocations especially of the spine and shoulder
  ▪ cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
  ▪ muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
  ▪ neurological: seizures and spinal cord damage
  ▪ ophthalmology: ocular compartment syndrome and cataract formation (late complication)
  ▪ renal: ATN resulting from toxic levels of myoglobin and hemoglobin
  ▪ vascular: vessel thrombosis → tissue necrosis (increased Cr, K⁺ and acidity), decrease in RBC (beware of hemorrhages/delayed vessel rupture)
**Treatment**
- ABCs, primary and secondary survey, treat associated injuries
- beware of cardiac arrhythmias (need to keep for monitoring)
- monitor: cardiac arrhythmia, hemochromogenuria, compartment syndrome, urine output
- wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
- debride non-viable tissue early and repeat prn (every 48 h) to prevent sepsis
- amputations frequently required

**FROSTBITE**
- see *Emergency Medicine, ER45*

---

## Hand

### Traumatic Hand

**Table 20. Key Features of the History and Physical Exam of the Injured Hand in the Emergency Department**

<table>
<thead>
<tr>
<th>Key Questions</th>
<th>Age</th>
<th>Hand dominance</th>
<th>Occupation</th>
<th>Time and place of accident</th>
<th>Mechanism of injury</th>
<th>Tetanus status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HISTORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PHYSICAL EXAM</strong></td>
<td>Structure</td>
<td>Examination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Observation</th>
<th>Position of finger</th>
<th>Deformity</th>
<th>Bruising or swelling</th>
<th>Sweating pattern</th>
<th>Anatomical structures beneath</th>
<th>Abnormal cadence (fingers normally slightly flexed), scissoring</th>
<th>Bony or specific (e.g. mallet, swan neck)</th>
<th>May indicate underlying skeletal injury</th>
<th>May indicate demervation</th>
<th>If open laceration, need to explore within wound (under sterile conditions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Status</td>
<td>Radial and ulnar arteries</td>
<td>Allen’s Test</td>
<td>Capillary refill (&lt;2-3 s)</td>
<td>For each test, need to compare both sides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory (refer to Figure 4)</td>
<td>Median nerve</td>
<td>Dorsal radial tip of index finger</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulnar nerve</td>
<td>Dorsal ulnar tip of little finger</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radial nerve</td>
<td>Dorsal web space of the thumb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Digital nerves</td>
<td>Z point discrimination of each finger</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor Function</td>
<td>Median nerve</td>
<td>Extrinsic muscles: flex DIP of index finger (“OK sign”)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulnar nerve</td>
<td>Extrinsic muscles: flex DIP of little finger Intrinsic muscles: abduct index finger (“Peace sign”) or patient able to hold piece of paper between adducted fingers and resist pulling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radial nerve</td>
<td>Extrinsic muscles: extend thumb (“thumb’s up”) and wrist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of Motion</td>
<td>Tendons, bones, joints, nerves</td>
<td>Assess active and passive range of motion of wrist extension/flexion/ulnar/radial deviation, finger abduction/adduction/flexion/extension, thumb flexion/extension/abduction/adduction/circumflexion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendons</td>
<td>FDP</td>
<td>Stabilize PIP in extension, ask patient to flex fingers (at DIP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FDS</td>
<td>Stabilize non-exam fingers in extension (neutralizes FDP) and ask patient to flex examination finger</td>
<td></td>
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<tr>
<td>Palpation</td>
<td>Bones</td>
<td>Focal tenderness or abnormal alignment</td>
<td></td>
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<tr>
<td></td>
<td>Joints</td>
<td>Instability may indicate ligamentous injury or dislocation</td>
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</tbody>
</table>

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*Allen’s Test: while patient’s hand is firmly closed, occlude both radial and ulnar arteries; once fist is open, release either artery and assess collateral flow

*Approach to Hand Lacerations
- TIN AX
- Tetanus prophylaxis
- Irrigate with NS (Copious irrigation and debridement in a timely manner)
- NPO (only if deeper structures are cut – i.e. needs an operation)
- Antibiotic prophylaxis (controversial – most require no ABx)
- X-rays

*Figure 22. Testing profundus (FDP) – inserts at distal phalanx
*Figure 23. Testing superficialis (FDS) – inserts at middle phalanx
General Management

Nerves
- test the nerve function BEFORE putting in local anesthesia
- direct repair for a clean injury within 14 d and without concurrent major injuries → otherwise secondary repair
- epineural repair of digital nerves with minimal tension
- post-operative: dress wound, elevate hand and immobilize
- Tinel's sign (cutaneous percussion over the repaired nerve) produces paresthesias and defines level of nerve regeneration
  - Wallerian degeneration occurs in the first 2 wk, which is why there is no Tinel's sign till after this time period
  - a peripheral nerve regenerates at 1 mm/d
  - paresthesias felt at area of percussion because re-growth of myelin (Schwann cells) is slower than axonal re-growth → percussion on exposed free-end of axon generates paresthesia

Vessels
- often associated with nerve injury (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 h
- dress, immobilize, and splint hand with finger tips visible
- monitor color, capillary refill, skin turgor, fingertip temperature post-revascularization

Tendons
- most tendon lacerations require primary repair
- many extensors are repaired in the emergency room, flexors are repaired in the operating room within 2 wk
- avoid excessive immobilization (specific protocols for flexors, 2-3 wk for extensors) to minimize stiffness and facilitate rehabilitation

Bones
- see Fractures and Dislocations, PL25

Nailbed
- remove nail to examine underlying nailbed under digital block anesthesia
- irrigate wound and nail thoroughly
- suture repair of nailbed with catgut suture
- replace cleaned nail, which acts as splint for any underlying distal phalangeal fracture and prevents adhesion formation between nail fold and nailbed

Hand Infections

Principles
- trauma is most common cause
- 5 cardinal signs: rubor (red), calor (hot), tumor (swollen), dolor (painful) and functio laesa (loss of function)
- 90% caused by Gram-positive organisms
- most common organisms (in order) – S. aureus, S. viridans, Group A Streptococcus, S. epidermidis, and Bacteroides melaninogenicus (MRSA is becoming more common)

TYPES OF INFECTIONS

Deep Palmar Space Infections
- uncommon, there are 9 spaces in the hand, the most commonly involved are thenar or mid-palm space (treated in the OR)

Felon
- definition: subcutaneous abscess in the fingertip that commonly occurs following a puncture wound into the pad of digit; may be associated with osteomyelitis (akin to compartment syndrome and can lead to skin necrosis
- treatment: elevation, warm soaks, cloxacillin 500 mg PO q6h (if in early stage); if obvious abscess then I&D, cultures/gram stain, PO cloxacillin

Flexor Tendon Sheath Infection
- Staphylococcus > Streptococcus > Gram-negative rods
- definition: acute suppurative tenosynovitis commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated
- clinical features: Kanavel’s 4 cardinal signs
  1. point tenderness along flexor tendon sheath (earliest and the most important)
2. severe pain on passive extension of DIP (second most important)
3. fusiform swelling of entire digit
4. flexed posture (increased comfort)

**treatment**
- OR incision and drainage, irrigation, IV antibiotics, and resting hand splint until infection resolves

**Herpetic Whitlow**
- HSV-1, HSV-2
- **definition:** painful vesicle(s) around fingertip
  - often found in medical/dental personnel and children
- **clinical features:** can be associated with fever, malaise and lymphadenopathy
  - patient is infectious until lesion has completely healed
- **treatment:** routine culture and viral prep protection (cover), consider oral acyclovir; do not break blisters, as this can spread infection

**Paronychia**
- acute = *Staphylococcus*; chronic = *Candida*
- **definition:** infection (granulation tissue) of soft tissue around fingernail (beneath eponychial fold)
- **etiology**
  - acute paronychia: a “hangnail”, artificial nails, and nail biting
  - chronic paronychia: prolonged exposure to moisture
- **treatment**
  - acute paronychia: warm compresses and cephalaxin 500 mg PO q6h if caught early and drainage if abscess present – can usually drain with a #11 blade directed into the abscess from underneath the paronychial fold
  - chronic paronychia: anti-fungals with possible debridement and marsupialization, removal of nail plate

### Amputations

**Hand or Finger**
- emergency management: injured patient and amputated part require attention
  - **patient:** x-rays, NPO, clean wound and irrigate with NS, dress stump with nonadherent, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/ erythromycin)
  - **amputated part:** x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice
- **indications for replantation**
  - **age:** children often better results than adults
  - **level of injury:** proximal, thumb and multiple digit amputations are higher priority
  - **nature of injury:** clean cut injuries have higher successful replantation rate; avulsion and crush injuries are relative contraindications to replant
  - if replant contraindicated manage stump with revision amputation
    - would only allow a fingertip injury to heal by secondary intention

### Tendons

**Common Extensor Tendon Deformities**

<table>
<thead>
<tr>
<th>Injury</th>
<th>Definition</th>
<th>Zone</th>
<th>Etiology/Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mallet Finger</strong></td>
<td>DIP flexed with loss of active extension</td>
<td>1</td>
<td>Forced flexion of the extended DIP leading to extensor tendon rupture at DIP (e.g. sudden blow to tip of the finger)</td>
<td>Splint DIP in extension for 6 wk followed by 2 wk of night splinting; if inadequate improvement after 6 wk, check splinting routine and recommend 4 more wk of continuous splinting</td>
</tr>
<tr>
<td><strong>Boutonniere Deformity</strong></td>
<td>PIP flexed, DIP hyperextended</td>
<td>3</td>
<td>Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx (laceration, volar dislocation, acute forceful flexion of PIP)</td>
<td>Splint PIP in extension and allow active DIP motion</td>
</tr>
<tr>
<td><strong>Swan Neck Deformity</strong></td>
<td>PIP hyperextended, DIP flexed</td>
<td>3</td>
<td>Trauma (PIP volar plate injury) Associated with RA and old, untreated mallet deformity</td>
<td>Splint to prevent PIP hyperextension or DIP flexion Consider arthrodesis/arthroplasty</td>
</tr>
</tbody>
</table>

[Figure 24. Zone of extensor tendon injury (odd numbered zones fall over a joint)]

[Figure 25. Mallet finger deformity]

[Figure 26. Boutonniere deformity]

[Figure 27. Swan neck deformity]
De Quervain’s Tenosynovitis (zone 7; most common cause of radial wrist pain)
  • **definition**: inflammation in 1st extensor compartment (APL and EPB)
  • **clinical features**
    - +ve Finkelstein’s test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)
    - pain localized to the 1st extensor compartment
    - tenderness and crepitation over radial styloid may be present
    - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)
  • **treatment**
    - mild: NSAIDs, splinting and steroid injection into the tendon sheath (successful in over 60% of cases)
    - severe: surgical release of stenotic tendon sheaths (APL and EPB); remember there may be 2 or more sheaths

Ganglion Cyst (zone 7)
  • **definition**
    - fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin
    - most common soft tissue tumor of hand and wrist (60% of masses)
  • **clinical features**
    - most common around scapholunate ligament junction
    - 3 times more common in women than in men
    - more common in younger individuals
    - can be large or small – may drain internally so size may wax and wane
    - often non-tender although tenderness increased when cyst smaller (from increased pressure within smaller cyst sac)
  • **treatment**
    - conservative treatment: watch and wait
    - aspiration (recurrence rate 65%)
    - consider operative excision of cyst and stalk (recurrence is possible)
    - steroids if painful

Common Flexor Tendon Deformities
  • flexor tendon zones (important for prognosis of tendon lacerations)
    - “no-man’s land”
      - between distal palmar crease and mid-middle phalanx
      - zone where superficialis and profundus lie ensheathed together
      - recovery of glide very difficult after injury

Stenosing Tenosynovitis (trigger finger/thumb)
  • **definition**: inflammation of synovium causes size discrepancy between tendon and sheath/pulley (most commonly at A-1 pulley) = locking of thumb or finger in flexion/extension
  • **etiology**: idiopathic or associated with RA, DM, hypothyroidism and gout
  • **clinical features**
    - thumb, ring and long fingers most commonly affected
    - patient complains of catching, snapping or locking of affected finger
    - tenderness to palpation/nodule at palmar aspect of MCP over A-1 pulley
    - women are 4 times more likely than men to be affected
  • **conservative treatment**
    - NSAIDs
    - steroid injection
    - surgical flexor tendon release
    - injections less likely to be successful in patients with DM or symptoms greater than 6 mo
  • **surgical treatment**
    - incise A-1 flexor tendon pulley to permit unrestricted, full active finger motion

Fractures and Dislocations
  • for fracture principles, see Orthopedics, OR5

**FRACTURES**
  • about 90% of hand fractures are stable in flexion (lock/prevent extension)
  • **position of function** (like a hand holding a pop can)
    - wrist extension 15°
    - MCP flexion 45°
    - IP flexion (slight)
    - thumb abduction/rotation
    - contraindications: post repair of flexor tendons, median/ulnar nerve injury
• position of safety
  - wrist extension 45° (position most beneficial for hand function if immobilized)
  - MCP flexion 60° (maximal collateral ligament stretch)
  - PIP and DIP in full extension (maximal volar plate origin stretch)
  - thumb abduction and opposition (functional position)
  - stiffness secondary to immobilization is the most important complication; Tx = early motion

Distal Phalanx Fractures
• most commonly fractured bone in the hand
• usual mechanism is crush injury and thus accompanied by soft tissue injury
• subungual hematoma is common and must be decompressed if painful or nail removed
• treatment consists of 3 wk of digital splinting (with IP joint movement preserved)

Proximal and Middle Phalanx Fractures
• check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit
• undisplaced or minimally displaced: closed reduction (if extra-articular) buddy tape to neighbouring stable digit, elevate hand, motion in guarded fashion early, splinted for 2-3 wk
• displaced, non-reducible, not stable with closed reduction, or rotational or scissoring deformity: percutaneous pins (K-wires) or ORIF, and splint

Metacarpal Fractures
• generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
• Boxer’s fracture (extra-articular): acute angulation of neck of metacarpal of little finger into palm
  - mechanism: blow on the distal-dorsal aspect of closed fist
  - loss of prominence of metacarpal head, volar displacement of head
  - check for scissoring of fingers on making a fist
  - up to 30-40° angulation may be acceptable
  - closed reduction should be considered to decrease the angle
  - if stable ulnar gutter splint for 2-3 wk with PIP and DIP free
• Bennett’s fracture (intra-articular): fracture/dislocation of the base of the thumb metacarpal
  - unstable fracture
  - abductor pollicis longus pulls MC shaft proximally and radially causing adduction of thumb
  - treat with percutaneous pinning, thumb spica x 6 wk
• Rolando’s fracture (intra-articular): T- or Y-shaped fracture of the base of the thumb metacarpal
  - treat with ORIF with K-wire

DISLOCATIONS
• must be reduced as soon as possible
• dislocation vs. subluxation
  - dislocation: severe injury where articular surfaces of a joint are no longer in contact with one another
  - subluxation: articular surfaces of a joint are partially out of place, but then go back into place (partial dislocation)

PIP and DIP Dislocations (PIP more common than DIP)
• usually dorsal dislocation (commonly from hyperextension)
• if closed dislocation: closed reduction and splinting (30° flexion for PIP and full extension for DIP) or buddy taping and early mobilization (prolonged immobilization causes stiffness)
• open injuries are treated with wound care, closed or open reduction and antibiotics

MCP Dislocations (relatively rare)
• dorsal dislocations much more common than volar dislocations
• dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
• two types of dorsal dislocation
  - simple (reducible with manipulation): treat with 2-4 wk of splinting at 30° MCP flexion
  - complex (volar plate blocks reduction): treat with open reduction and A1 pulley release + extension-blocking splint at 30° flexion (2 wk) then 10° flexion (2 wk)

Ulnar Collateral Ligament (UCL) Injury
• forced abduction of thumb (e.g. ski pole injury)
• skier’s thumb: acute UCL injury
• gamekeepers thumb: chronic UCL injury
• evaluation: radially deviate joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion
• Stener’s lesion: the UCL has bony attachments to the adductor aponeurosis and the proximal ligament can displace while the distal attachment remains deep to the aponeurosis, forming a barrier that blocks healing and leads to chronic instability; requires surgery
**Dupuytren’s Disease**

**Definition**
- contraction of longitudinal palmar fascia, forming nodules (usually painless), fibrous cords and eventually flexion contractures at the MCP and interphalangeal joints
- flexor tendons not involved
- Dupuytren’s diathesis: early age of onset, strong family history, and involvement of sites other than palmar aspect of hand

**Epidemiology**
- genetic disorder, unusual in patients from African and Asian countries, high incidence in northern Europeans, men > women, often presents in 5th-7th decade of life, associated with but not caused by alcohol use and DM

**Clinical Features**
- order of digit involvement (most common to least common): ring > little > long > thumb > index
- may also involve feet (Ledderhose’s) and penis (Peyronie’s – see Urology, U29)

**Treatment**
- stages
  1. palmar pit or nodule: no surgery
  2. palpable band/cord with no limitation of extension of either MCP or PIP: no surgery
  3. lack of extension at MCP or PIP: surgical fasciectomy indicated
  4. irreversible periarticular joint changes/scarring: surgical treatment possible but poorer prognosis compared to stage 3

- indications for percutaneous release
  - functional impairment
  - MCP contractures >30°
  - any PIP contracture
  - rapidly progressive disease
- may recur, especially in Dupuytren’s diathesis

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**Carpal Tunnel Syndrome**

**Definition**
- median nerve compression at the level of the flexor retinaculum as opposed to pronator teres syndrome

**Etiology**
- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumors, hypertrophic synovial tissue, fracture callus, and osteophytes), metabolic and physiological (pregnancy, hypothyroidism, acromegaly, and RA), infections, neuropathies (associated with DM or alcoholism), and familial disorders
- job/hobby related repetitive trauma, especially forced wrist flexion

**Epidemiology**
- female:male = 4:1, most common entrapment neuropathy

**Clinical Features**
- sensory loss in median nerve distribution i.e. radial 3.5 digits (see Figure 4)
- discriminative touch often lost first
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/rubbing
- decreased light touch and 2-point discrimination, especially fingertips
- ± Tinel’s sign (tingling sensation on percussion of nerve)
- ± Phalen’s sign (wrist flexion induces symptoms)

**Investigations**
- clinical diagnosis
- NCV and EMG may confirm, but do not exclude, the diagnosis

**Treatment**
- avoid repetitive wrist and hand motion, wrist splints when repetitive wrist motion required
- conservative: night time splinting to keep wrist in neutral position
- medical: NSAIDs, local corticosteroids injection, oral corticosteroids
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: numbness and tingling ± sensory loss, weakness ± muscle atrophy, unresponsive to conservative measures
- complications of surgery; injury to median motor branch, palmar cutaneous branch or superficial transverse vascular arch, local pain (pillar pain), and scar formation

---

**Accuracy of the Clinical Assessment for Carpal Tunnel Syndrome**

- **Phalen’s**
  - Sensitivity: 0.75
  - Specificity: 0.47

- **Tinel’s**
  - Sensitivity: 0.60
  - Specificity: 0.67

**Development and Validation of Diagnostic Criteria for Carpal Tunnel Syndrome**

*J Hand Surg* 2006;31:919-924

**Purpose**: To develop a clinical diagnostic criteria for carpal tunnel syndrome that modeled the clinical diagnostic practices of experts.

**Methods**: Out of 57 clinical findings associated with CTS, eight were ranked highly by a panel of expert clinicians. Using 256 case histories, a panel of experts decided whether a case did or did not have a diagnosis of CTS. This diagnosis represented the dependent variable for a logistic regression model, to which the eight clinical findings were applied. The regression model was then validated against the consensus of a second panel on the diagnosis of CTS for the case histories.

**Results/Conclusions**: The correlation between the probability of CTS predicted by the regression model and the panel of clinicians was 0.71. Clinical diagnostic criteria that contributed significantly to the model were:

1. Numbness and tingling in median nerve distribution
2. Nocturnal numbness
3. Weakness and/or atrophy of the thenar musculature
4. Tinel’s sign
5. Phalen’s test
6. Loss of 2-point discrimination
### Rheumatoid Hand

- see Rheumatology, RH5

### Brachial Plexus

#### Etiology
- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumors, ectopic ribs

#### Common Palsies

<table>
<thead>
<tr>
<th>Table 22. Named Neonatal Palsies of the Brachial Plexus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palsy</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Duchenne-Erb Palsy</td>
</tr>
<tr>
<td>Klumpke's Palsy</td>
</tr>
</tbody>
</table>

#### Differential Diagnosis
- trauma (blunt, penetrating)
- thoracic outlet syndrome
  - neurogenic: associated with cervical rib; compression of C8/T1
  - vascular: pain or sensory symptoms without cervical rib; cessation of radial pulse with provocative maneuvers
- tumor
  - schwannoma: well-defined margins makes it easier for total resection
  - neurofibromas: associated with neurofibromatosis type I
  - other: e.g. Pancoast syndrome (apical lung tumor)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

#### Investigations
- EMG
- MRI: gold standard for identifying soft tissue masses
- CT myelogram: better than MRI for identification of nerve root avulsion and identification of pseudomeningocoele. Important for pre-operative identification of patients likely to require neurotisation procedures (especially for patients with blunt trauma)

#### Management

<table>
<thead>
<tr>
<th>Table 23. Management of Brachial Plexus Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>Non-Penetrating Trauma</td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Penetrating Trauma</td>
</tr>
</tbody>
</table>

### Craniofacial Injuries

- low velocity vs. high velocity injuries determine degree of damage
- fractures cause bruising, swelling and tenderness → loss of function
- frequency: nasal > zygomatic > mandibular > maxillary
- management: can wait 5-10 d for swelling to decrease before ORIF required
Approach to Facial Injuries

• ATLS protocol
• inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve)
• visual assessment
• tetanus prophylaxis
• radiological evaluation
• wound irrigation with NS/RL and remove foreign materials
• conservative debridement of detached or nonviable tissue
• repair when patient's general condition allows (soft tissue injury: <8 h preferable)

Investigations

• CT
  • axial and coronal (specifically request 1.5 mm cuts): for fractures of upper and middle face (not good for mandible)
  • indicated for high velocity trauma, complex facial fractures, orbital floor, panface fractures, pre-operative assessment
• panorex radiograph: shows entire upper and lower jaw; best for isolated mandible fracture as patient must be able to sit

Table 24. Imaging of the Craniofacial Skeleton

<table>
<thead>
<tr>
<th>Structure</th>
<th>Appropriate Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandible</td>
<td>Panoramic (panorex)*</td>
</tr>
<tr>
<td></td>
<td>CT *</td>
</tr>
<tr>
<td>Zygomatic and Orbital Bones</td>
<td>CT scan*</td>
</tr>
<tr>
<td></td>
<td>Water’s view (occipitomental, A-P “from below”), Town’s, AP</td>
</tr>
<tr>
<td>Nasal Bones</td>
<td>No x-ray required – clinical</td>
</tr>
<tr>
<td>Maxilla</td>
<td>CT scan* – axial and coronal</td>
</tr>
</tbody>
</table>

*Gold standard

Treatment

• consultation when indicated (dentistry, ophthalmology)
• re-establish normal occlusion
• pursue normal eye function
• restore stability of face and appearance

Complications

• diplopia/enophthalmas/blindness
• intracranial pathology such as CSF leak, bleeding and SIADH
• sinusitis
• functional abnormalities (i.e. malocclusion)
• infection – extremely rare
• poor cosmesis; need for 2nd surgery
• septal hematoma and septal necrosis

Mandibular Fractures

• always two points of injury since it is a ring structure (includes fractures and dislocations)
• commonly at sites of weakness (condylar neck, angle of mandible, region of 3rd molar or canine tooth)

Etiology

• anterior force: bilateral fractures
• lateral force: ipsilateral subcondylar and contralateral angle or body fracture
• note: classified as open if fracture into tooth bearing area (alveolus)

Clinical Features

• pain, swelling, difficulty opening mouth ("trismus")
• malocclusion, asymmetry of dental arch
• damaged, loose, or lost teeth
• palpable "step" along mandible
• numbness in V3 distribution
• intra-oral lacerations or hematoma (sublingual)
• chin deviating toward side of a fractured condyle
• bilateral condyle fractures will have anterior open bite
Classification

Table 25. Mandibular Fracture Classifications by Anatomic Region (refer to Figure 35)

<table>
<thead>
<tr>
<th>Areas/Boundaries</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symphysis</td>
<td>Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible</td>
</tr>
<tr>
<td>Body*</td>
<td>From the symphysis to the distal alveolar border of the third molar</td>
</tr>
<tr>
<td>Angle</td>
<td>Triangular region between the anterior border of the masseter and the posteroinferior insertion of the masseter distal to the third molar</td>
</tr>
<tr>
<td>Ramus</td>
<td>Part of the mandible that extends posteroinferiorly into the condylar and coronoid processes</td>
</tr>
<tr>
<td>Condylar</td>
<td>Area of condylar process of mandible</td>
</tr>
<tr>
<td>Subcondylar</td>
<td>Area below the condylar neck (i.e. sigmoid notch) of the mandible</td>
</tr>
<tr>
<td>Coronoid Process</td>
<td>Area of the coronoid process of mandible</td>
</tr>
</tbody>
</table>

*Most common mandibular fracture type

Treatment
- maxillary and mandibular arch bars wired together (intramaxillary fixation) or ORIF
- antibiotics to cover against S. aureus and anaerobes

Complications
- malocclusion, malunion
- tooth loss, and possible sensation loss
- TMJ ankylosis

Maxillary Fractures

Table 26. Le Fort Classification (refer to Figure 36)

<table>
<thead>
<tr>
<th>Le Fort I</th>
<th>Le Fort II</th>
<th>Le Fort III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative Name</td>
<td>Guérin fracture</td>
<td>Pyramidal fracture</td>
</tr>
<tr>
<td>Type of Fracture</td>
<td>Horizontal</td>
<td>Pyramidal</td>
</tr>
<tr>
<td>Structures Involved</td>
<td>Piriorm aperture</td>
<td>Nasal bones</td>
</tr>
<tr>
<td></td>
<td>Maxillary sinus</td>
<td>Medial orbital wall</td>
</tr>
<tr>
<td></td>
<td>Pterygoid plates</td>
<td>Maxilla</td>
</tr>
<tr>
<td></td>
<td>Pterygoid plates</td>
<td>Pterygoid plates</td>
</tr>
<tr>
<td>Anatomical Result</td>
<td>Maxilla divided into 2 segments</td>
<td>Maxillary teeth separated from face</td>
</tr>
</tbody>
</table>

Nasal Fractures

Etiology
- lateral force → more common, good prognosis
- anterior force ← can produce more serious injuries
- most common facial fracture

Clinical Features
- epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum, crepitus, septal hematoma, respiratory obstruction, subconjunctival hemorrhage
- depression and splaying of nasal bones causing a saddle deformity
- important to clinically assess for naso-orbital ethmoid fractures

Treatment
- in the absence of complications, no treatment required
- closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with Adaptic®, nasal splint for 7 d
- best reduction immediately (<6 h) or when swelling subsides (5-7 d)
- rhinoplasty may be necessary later for residual deformity (30%)
Naso-Orbital Ethmoid Fractures

Etiology
- fractures of the nasal and ethmoid bones of the medial orbit
- problematic and may lead to greatest change in facial appearance
- Markowitz-Manson classification
  - Type 1: Single, central fragment, medial canthal ligament intact
  - Type 2: Comminuted central fragment, medial canthal ligament intact
  - Type 3: Severe comminution of central fragment and disrupted medial canthal ligament

Clinical Presentation
- telecanthus (increased intercanthal distance secondary to medial canthal ligament disruption)
- orbital rim step-off
- similar to nasal fractures

Treatment
- surgical repair to restore intercanthal distance, nasal projection and orbital anatomy

Zygomatic Fractures

- 3 categories
  1. fracture restricted to zygomatic arch
  2. depressed fracture of zygomatic complex (zygoma)
  3. unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone and orbital rim

Clinical Features
- flattening of malar prominence (view from above)
- pain over fractures on palpation
- numbness in V2 distribution (infraorbital and superior dental nerves)
- palpable step deformity in bony orbital rim (especially inferiorly)
- often associated with fractures of the orbital floor
- ipsilateral epistaxis; trismus (lock jaw)

Treatment
- if undisplaced, stable and no symptoms, then soft diet; no treatment necessary
- ophthalmologic evaluation if suspected orbital injury
- uncomplicated zygomatic arch fractures can be elevated using Gillies approach: leverage on the anterior part of the zygomatic arch via a temporal incision; stabilization often unnecessary
- ORIF for displaced or unstable fractures of zygomatic complex

Orbital Floor Fractures

- see Ophthalmology, OP43

Definition
- fracture of floor of orbit ± intact infraorbital rim
- may be associated with nasoethmoid fracture

Etiology
- blunt force to eyeball → sudden increase in intra-orbital pressure (e.g. baseball or fist)

Clinical Features
- check visual fields and acuity for injury to globe
- periorbital edema and bruising, subconjunctival hemorrhage
- ptosis, exophthalmos, exorbitism, or enophthalmos
- orbital rim step-offs with possible infraorbital nerve anesthesia
- vertical dystopia (abnormal displacement of the entire orbital cone in the vertical plane); diplopia looking up or down (entrapment of inferior rectus), limited EOM
- orbital entrapment
  - clinical diagnosis that is a surgical emergency
  - diplopia with vertical gaze; limited EOM
  - severe pain or nausea and vomiting with eye movement
  - requires urgent ophthalmology evaluation and surgical repair
Investigations
- CT (diagnostic): axial and coronal views
- diagnostic manoeuvre for entrapment is forced duction test (pulling on inferior rectus muscle with forceps to ensure full ROM) under anesthesia

Treatment
- surgical repair indicated if: urgent repair for entrapment, floor defect >1 cm, any size defect with enophthalmos or persistent diplopia (>10 d)
- reconstruction of orbital floor with bone graft or alloplastic material
- ophthalmologic evaluation suggested

Complications
- persistent diplopia
- enophthalmos

Superior Orbital Fissure Syndrome
- fracture of SOF causing ptosis, proptosis, anesthesia in V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, V1)
- uncommon complication seen in Le Fort II and III fractures (1/130)
- recovery time reported as 4.8-23 wk following operative reduction of fractures

Orbital Apex Syndrome
- fracture through optic canal with involvement of CN II at apex of orbit
- symptoms are the same as SOF syndrome plus vision loss
- treatment is urgent decompression of fracture in optic canal or steroids (emergency)

Breast Surgery

Breast Reconstruction

- integral part of breast cancer treatment
- two basic methods: implants (1-stage or 2-stage) or autologous tissue
- may also require breast balancing procedure and nipple areola reconstruction

Pre-Reconstruction Considerations
- radiation: treatment before and after mastectomy is a relative contraindication to alloplastic reconstruction
- recipient tissue: skin sparing mastectomy allows for the use of implants without tissue expanders (1-stage process)
- donor tissue: limited availability of suitable donor tissue (lack of tissue, scar, previous surgery that interferes with blood supply) may prevent the use of autologous tissue reconstruction
- timing (immediate vs. delayed)
- contralateral breast: may not be possible to reconstruct a breast of the same size or shape as the contralateral breast. Breast reduction or mastopexy may be considered in opposite breast (see Table 28)
- other considerations: patient’s age and comorbidities, prognosis, body weight, characteristics of chest wall and patient’s attitude

Table 27. Options for Breast Reconstruction

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Definition</th>
<th>Surgical Details</th>
<th>Other Comments</th>
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<tr>
<td>Alloplastic (Implant based)</td>
<td>Use of synthetic material (silicone or saline implants)</td>
<td>With expanders (2 stages): Use tissue expanders before replacement with implants to help facilitate breast ptosis Without expanders (1 stage): In skin-sparing mastectomy, enough skin is available for immediate placement of implant (may require acellular dermal matrix if implant size and muscle size is a mismatch)</td>
<td>Complications: capsular contraction (foreign body reaction to implants), rupture or leakage of implant, increased risk of infection, 35% revision rate over 5 yr</td>
</tr>
<tr>
<td>Autologous Tissue</td>
<td>Use of patient’s own tissue</td>
<td>Many flap options: DIEP, TRAM, latissimus dorsi, SIEA, SGAP, and IGAP</td>
<td>Offers reduced long-term morbidity and natural consistency</td>
</tr>
<tr>
<td>Nipple Areola Reconstruction</td>
<td>Final stage of breast reconstruction</td>
<td>Usually require tattooing for areola reconstruction Local vs. distant flap/graft: 1. Local: fish tail or skate flap most common; these flaps allow simultaneous nipple and areola reconstruction 2. Distant: opposite nipple, earlobe, abdominal skin, costal cartilage, labia</td>
<td>Usually performed 3 mo post-reconstruction</td>
</tr>
</tbody>
</table>

Diplopia can present late in orbital blow-out fractures

Patients may require a balancing procedure on contralateral side
Breast Tissue Expanders

- placement: sub-pectoral, total submuscular (pectoral/serratus)
- size: depends on contralateral breast and desired size
  - generally over-expanded to facilitate ptosis
- timing of expansion: begins when wound fully healed (usually 2 wk post-operative), and implants are expanded weekly or bi-weekly until complete (up to 3 mo); expanders are exchanged for implants after another 3 mo for consolidation of expanded skin

Arterial blood supply to the breast

- internal thoracic*
- external thoracic*
- lateral thoracic
  - thoracoacromial
  - intercostals
  - thoracodorsal
* also provide arterial blood supply to nipple-areola complex

Pedicle Designs

- inferior pedicle technique
- superior pedicle
- central pedicle/mound
- medial pedicle

Breast Reduction

- reduction mammoplasty performed for relief of physical symptoms (e.g. shoulder groove, neck pain, back pain, shoulder pain, mastodynia), and to improve breast size and shape
- key steps of procedure
  - incisions: circular around the areola, vertical from areola incision to infra-mammary fold, along the natural infra-mammary fold
  - removal of fat, breast tissue, and excess skin
  - possible need to move nipple and areola complex to higher position
- complications: infection, hemorrhage, decreased nipple sensation, inability to breast feed, breast/nipple asymmetry, nipple loss (partial or complete), skin loss/necrosis, fat necrosis


**Purpose:** To determine if breast augmentation for cosmetic purposes affects stage at diagnosis and post-diagnosis survival compared with women with no implants.

**Methods:** Systematic review of observational studies with two meta-analyses.

**Results:** Meta-analysis examining breast CA stage:
- odds ratio 1.26 for non-localized stage breast CA at diagnosis comparing women with and without implants (12 studies, 95% CI 0.99-1.6; p=0.05).
- Meta-analysis examining post-diagnosis survival:
  - reduced survival after breast CA among women with implants compared with women without implants (5 studies, hazard ratio for breast CA specific mortality 1.38, CI 1.08-1.75).

**Conclusions:** Although findings need to be interpreted with caution, research published to date suggests that cosmetic breast augmentation may adversely affect survival of women subsequently diagnosed with breast CA.
# Aesthetic Surgery

## Aesthetic Procedures

<table>
<thead>
<tr>
<th>Location</th>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/Neck</td>
<td>Hair transplants</td>
<td>Aesthetic improvement of hair growth patterns using grafts or flaps</td>
</tr>
<tr>
<td></td>
<td>Otoplasty</td>
<td>Surgical correction of protruding ears</td>
</tr>
<tr>
<td></td>
<td>Brow lift</td>
<td>Surgical procedure to lift low brows</td>
</tr>
<tr>
<td>Face</td>
<td>Rhytidectomy</td>
<td>Surgical procedure to reduce wrinkling and sagging of the face and neck; “face lift”</td>
</tr>
<tr>
<td></td>
<td>Blepharoplasty</td>
<td>Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin ± fat pads</td>
</tr>
<tr>
<td></td>
<td>Rhinoplasty</td>
<td>Intranasal surgical reconstruction of the nose</td>
</tr>
<tr>
<td></td>
<td>Genioplasty</td>
<td>Chin augmentation via osteotomy or synthetic implant to improve contour</td>
</tr>
<tr>
<td></td>
<td>Lip augmentation</td>
<td>Procedure to create fuller lips and to reduce wrinkles around the mouth using collagen injections, fat transferred from other body parts, or implantable materials</td>
</tr>
<tr>
<td>Skin</td>
<td>Chemical peel</td>
<td>Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration</td>
</tr>
<tr>
<td></td>
<td>Dermabrasion</td>
<td>Skin re-surfacing by sanding with a rapidly rotating abrasive tool; often used to reduce scars, irregular skin surfaces and fine lines</td>
</tr>
<tr>
<td></td>
<td>Laser resurfacing</td>
<td>Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening; often used to reduce scars and wrinkles</td>
</tr>
<tr>
<td></td>
<td>Injectable fillers</td>
<td>An injectable substance is used to decrease frown lines, wrinkles, and nasolabial folds; substances include collagen, fat, hyaluronic acid, and calcium hydroxyapatite</td>
</tr>
<tr>
<td>Other</td>
<td>Abdominoplasty</td>
<td>Removal of excess skin and repair of rectus muscle laxity (rectus diastasis); “tummy tuck”</td>
</tr>
<tr>
<td></td>
<td>Breast augmentation</td>
<td>Surgical breast enhancement with silicone or saline implants</td>
</tr>
<tr>
<td></td>
<td>Calf augmentation</td>
<td>Augmentation of calf muscle with implants</td>
</tr>
<tr>
<td></td>
<td>Liposuction</td>
<td>Surgical removal of adipose tissue for body contouring (not a weight loss procedure)</td>
</tr>
<tr>
<td></td>
<td>Mastopexy</td>
<td>Surgical breast lift to elevate breast mound and tighten the skin envelope in ptotic breasts</td>
</tr>
<tr>
<td></td>
<td>Breast reduction</td>
<td>Surgical breast reduction for relief of physical symptoms</td>
</tr>
<tr>
<td></td>
<td>Sclerotherapy</td>
<td>Injection with a sclerosant to treat telangiectasias and varicose veins</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia</td>
<td>Excessive development of male mammary glands; Treated with traditional or ultrasound-assisted liposuction</td>
</tr>
</tbody>
</table>

Figure 39. Augmentation mammoplasty: incision lines and implant placement
### Craniofacial Anomalies

#### Table 29. Pediatric Craniofacial Anomalies

<table>
<thead>
<tr>
<th>Definition</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft Lip</td>
<td>Failure of fusion of maxillary and medial nasal processes M:F = 2:1</td>
<td>Classified as incomplete/complete and uni/bilateral 2/3 cases: unilateral, left-sided, male</td>
<td>Surgery (3 mo): Milliard, Tenison-Randall, or Fisher subunit repair corrections usually required later on (especially for nasal deformity)</td>
</tr>
<tr>
<td>Cleft Palate</td>
<td>Failure of fusion of lateral palatine/median palatine processes and nasal septum Isolated cleft palate: 0.5 per 1,000 (no racial variation) F&gt;M</td>
<td>Classified as incomplete/complete and uni/bilateral Isolated (common in females) or in conjunction with cleft lip (common in males)</td>
<td>Special bottles for feeding Speech pathologist Surgery (6-9 mo): Von Langenbeck or Furlow Z-Plasty ENT consult – often recurrent otitis media, requiring myringotomy tubes</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>Premature fusion of ≥1 cranial sutures Primary – abnormal suture, no known cause This may limit brain growth perpendicular to the suture and cause compensatory growth parallel to the fused suture 1 in 2,000 live newborns; M:F = 52:48 Syndromes include: Crouzon’s, Apert’s, Saethre-Chotzen, Carpenter’s, Pfeiffer’s-Jackson-Weiss and Boston-type syndromes</td>
<td>Syndromic – associated with genetic mutation Secondary (to microcephaly, hypertelorism, rickets, etc.) Dx: irregular head shape, craniofacial abnormalities, x-ray</td>
<td>Multidisciplinary team (including neurosurgery, ENT, genetics, dentistry, pediatrics, SLP) Early surgery prevents secondary deformities ↑ ICP is an indication for emergent surgery ICU bed may be required post-surgically</td>
</tr>
</tbody>
</table>

### Congenital Hand Anomalies

#### Table 30. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of Formation</td>
<td>Transverse absence (congenital amputation)</td>
<td>At any level (often below elbow/wrist)</td>
<td>Early prosthesis</td>
</tr>
<tr>
<td></td>
<td>Longitudinal absence (phocomelia)</td>
<td>Absent humerus Thalidomide association</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radial deficiency (radial club hand)</td>
<td>Radial deviation Thumb hypoplasia M&gt;F</td>
<td>Physiotherapy ± splinting Soft tissue release if splinting fails Distraction osteogenesis (Ilizarov) ± wedge osteotomy Tendon transfer Pollicization</td>
</tr>
<tr>
<td></td>
<td>Thumb hypoplasia</td>
<td>Degree ranges from small thumb with all components to complete absence</td>
<td>Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger</td>
</tr>
<tr>
<td></td>
<td>Ulnar club hand</td>
<td>Rare, compared to radial club hand Stable wrist</td>
<td>Splinting and soft-tissue stretching therapies Soft-tissue release (if above fails) Correction of angulation (Ilizarov distraction)</td>
</tr>
<tr>
<td></td>
<td>Cleft hand</td>
<td>Autosomal dominant Often functionally normal (depending on degree)</td>
<td>First web space syndactyly release Osteotomy/tendon transfer of thumb (if hypoplastic)</td>
</tr>
<tr>
<td>Classification</td>
<td>Example</td>
<td>Features</td>
<td>Treatment</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Failure of Differentiation/</td>
<td>Syndactyly</td>
<td>Fusion of ≥2 digits 1/3,000 live births MLP = 2:1</td>
<td>Surgical separation before 6-12 mo of age Usually good result</td>
</tr>
<tr>
<td>Separation</td>
<td></td>
<td>Classified as partial/complete Simple (skin only) vs. complex (osseous or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cartilaginous bridges)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symbrochactyly</td>
<td>Short fingers with short nails at fingertips</td>
<td>Digital separation (more difficult) Webspace deepening</td>
</tr>
<tr>
<td>Camptodactyly</td>
<td></td>
<td>Congenital flexion contracture (usually at PIP, especially 5th digit)</td>
<td>Early splinting Volar release Arthroplasty (rarely)</td>
</tr>
<tr>
<td></td>
<td>Clinodactyly</td>
<td>Radial or ulnar deviation Often middle phalanx</td>
<td>None (usually); if severe, osteotomy with grafting</td>
</tr>
<tr>
<td></td>
<td>Polyactyly</td>
<td>Congenital duplication of digits May be radial (increased in Aboriginals and</td>
<td>Amputation of least functional digit Usually &gt; 1 yr of age (when functional status can be assessed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asians) or central or ulnar (increased in Blacks)</td>
<td></td>
</tr>
<tr>
<td>Overgrowth</td>
<td>Macrodactyly</td>
<td>Rare</td>
<td>None (if mild) Soft tissue/bony reduction</td>
</tr>
<tr>
<td>Undergrowth</td>
<td>Brachyactyly</td>
<td>Short phalanges</td>
<td>Removal of non-functional stumps Osteotomies/lendon transfers Distraction osteogenesis Phalangeal/free toe transfer</td>
</tr>
<tr>
<td></td>
<td>Symbrochactyly</td>
<td>(brachysyndactyly)</td>
<td>As above + syndactyly release</td>
</tr>
<tr>
<td>Constriction Band Syndrome</td>
<td>i.e. amniotic (amnial) band syndrome</td>
<td>Variety of presentations</td>
<td>Urgent release for acute, progressive edema distal to band in newborn Other reconstruction is case-specific</td>
</tr>
<tr>
<td>Generalized Skeletal Abnormality</td>
<td>Achondroplasia, Marfan’s,</td>
<td>Variety of presentations</td>
<td>Treatment depends on etiology</td>
</tr>
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**Historical Context of Public Health**

- see [Ethical, Legal, and Organizational Medicine](#), ELOAM2 for Legal Foundation

**Definitions**

- **population health**
  - health of the population as measured by health status indicators (e.g. life expectancy, low birth weight rates)
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviors; health care services
  - refers to the prevailing or desired level of health in the population of a specific country/region/subset of population
  - considered to be more complex than the aggregate health status of individuals within a population

- **public health**
  - organized collective efforts of society to protect, promote, and restore the health of the public and prevent illness, injury, and premature death
  - refers to the practices, programs, policies, institutions, and disciplines required to achieve the desired state of population health

- **public health and preventive medicine** (formerly called community medicine)
  - the postgraduate study of health and disease in the population or a specified community
  - goal: to identify and address health problems and evaluate the extent to which health services and others address these issues


**Determinants of Health**

**Concepts of Health**

- **wellness**: state of dynamic physical, mental, social, and spiritual well-being that enables a person to achieve full potential and have an enjoyable life
- **disease**: abnormal, medically-defined changes in the structure or function of the human body
- **illness**: an individual’s experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles
- **illness behavior**: an individual’s actions in response to their illness, including whether they seek health care and whether they comply with the subsequent recommendations
- **sickness**: socially and culturally held conceptions of health conditions that may influence how the patient reacts
- **impairment**: any loss or abnormality of psychological, physiological, or anatomical structure or function
- **disability**: any restriction or lack of ability to perform an activity within the range considered normal for a human being
- **handicap**: the disadvantage for an individual arising due to impairment and disability
  - limits or prevents the fulfillment of an individual’s normal role as determined by society and depends on age, sex, social, and cultural factors
  - changes the individual’s relationship with the physical and social environment

- **health equity**: when all people have “the opportunity to attain their full health potential” and no one is “disadvantaged from achieving this potential because of their social position or other socially determined circumstance.” Differs from health equality. Health inequalities are those which are considered unjust and/or avoidable

- **health equality**: defined as where populations have equal or similar health status. Health inequalities are systematic differences in health status that occur among population groups

Source: Public Health Agency of Canada
Determinants of Health

Figure 1. Population health model

Table 1. Health Determinants of Vulnerable Populations

<table>
<thead>
<tr>
<th>Vulnerable Populations</th>
<th>Definition</th>
<th>Psychosocial/Socioeconomic</th>
<th>Physical Environment</th>
<th>Individual Behavior</th>
<th>Population-Specific Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indigenous Peoples</td>
<td>Persons having origins in any of the original peoples of North America and who maintains tribal affiliation or community attachment</td>
<td>Low income Family violence Low education status Unemployment Homelessness Longer length of disability</td>
<td>Crowded housing Inefficient ventilation Environmental toxins (botulism) TB declining but prevalence higher than rest of population</td>
<td>Smoking Substance misuse Excessive gambling Poor nutrition Sedentary lifestyle High BMI Higher risk of suicide</td>
<td>Mental health awareness Indigenous-specific diabetes initiatives Substance abuse treatment programs</td>
</tr>
<tr>
<td>Isolated Seniors</td>
<td>Individuals &gt; 65 yr Elder abuse Lack of emotional support</td>
<td>Low hazard tolerance Institutionalization Mobility issues Elder abuse Low income Long term care needs</td>
<td>Inactivity Polypharmacy Medical comorbidities</td>
<td>Aging in place of choice Falls and injury prevention Mental health promotion Preventing abuse and neglect</td>
<td></td>
</tr>
<tr>
<td>Children in Poverty</td>
<td>Based on Low Income Cut Offs (LICO) LICO is an income threshold below which a family will likely devote a large share of its income on the necessities of food, shelter and clothing than the average family</td>
<td>Low income Family dysfunction Lack of educational opportunities Housing availability Unsafe housing Lack of recreational space</td>
<td>Poor supervision Food insecurity High risk behaviors</td>
<td>Improvements in family income most significant Early childhood education</td>
<td></td>
</tr>
<tr>
<td>People with Disabilities</td>
<td>Includes impairments, activity limitations, and participation restrictions</td>
<td>Low income Low education status Discrimination Institutionalization Barriers to access Transportation challenges</td>
<td>Substance misuse Poor nutrition Inactivity Dependency for ADLs</td>
<td>Transportation support Multidisciplinary care Unique support for individuals with specific disabilities (e.g. Trisomy 21)</td>
<td></td>
</tr>
<tr>
<td>New Immigrants</td>
<td>Person born outside of the United States who has been granted the right to live in United States permanently by immigration authorities</td>
<td>Access to community services Cultural perspectives Diseases and conditions in country of origin (e.g. smoke from wood fires, incidence of TB, etc.)</td>
<td>Employment, ESL Healthy Newcomer Effect (health worsens over time to match that of the general population) Cultural or religious expectations</td>
<td>Women's health Mental health Infectious diseases (syphilis blood test, CXR, HIV) Dental and vision screening Vaccinations Cancer screening</td>
<td></td>
</tr>
</tbody>
</table>

Definitions of Health
- First multidimensional definition of health, as defined by the WHO in 1948: “state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”
- WHO updated the definition (socio-ecological definition) of health in 1986: “The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities” (Ottawa Charter for Health Promotion)
- Other definitions of health have since been proposed that incorporate other dimensions of health (e.g. “Health is a social, economic, and political issue and above all a fundamental human right” – The People’s Charter for Health)
Table 1. Health Determinants of Vulnerable Populations (continued)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Psychosocial/ Socioeconomic</th>
<th>Physical Environment</th>
<th>Individual Behavior</th>
<th>Population-Specific Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Homeless Persons</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>An individual who lacks permanent housing</td>
<td>Low income Mental illness</td>
<td>Exposure to temperature extremes Infections such as West Nile Virus</td>
<td>Substance misuse Violence</td>
<td>Safe housing Addictions support Mental health</td>
</tr>
<tr>
<td><strong>Refugee Health</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced to flee country of origin because of a well-founded fear of persecution and given protection by the Government of the United States</td>
<td>Post-traumatic stress disorders Depression Adjustment problems IFH (Interim Federal Health) for refugee claimants, health coverage 1 yr for medical necessities, specifically does not cover screening or preventative care</td>
<td>Diseases and conditions in country of origin (e.g. malaria, TB, onchocerciasis, etc.) Direct and indirect effects of war</td>
<td>Employment ESL Longstanding prior lack of access to health care (chronically neglected problems) Cultural or religious expectations</td>
<td>Vaccinations Women’s health Mental health Infectious diseases Dental and vision screening Political advocacy</td>
</tr>
</tbody>
</table>

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population

Disease Prevention

Disease Prevention Strategies
• measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

Primary Prevention
• implemented to prevent disease from occurring
• immunization programs exist in most countries to address major causes of pediatric morbidity and mortality that are preventable by vaccines, e.g. measles, diphtheria, pertussis, tetanus, polio, and tuberculosis (not routine in the U.S.)
• additional immunizations are offered in US depending on jurisdiction: mumps, rubella, rotavirus, hepatitis B, Haemophilus influenzae type B, varicella, HPV, conjugated pneumococcal and meningococcal vaccines (see Pediatrics, P3)

Secondary Prevention (Screening)
• presumptive identification (not diagnosis) of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly
• types of screening
  ▪ mass screening: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
  ▪ selective screening: screening of a specific subgroup of the population at risk for a disease (e.g. mammography in women >50 yr old)
  ▪ multiphasic screening: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)

Table 2. Ideal Criteria for Screening Tests

<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
<th>Health Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes significant suffering and/or death Natural history must be understood Must have an asymptomatic stage that can be detected by a test Early detection and intervention must result in improved outcomes Incidence is not too high or too low</td>
<td>High specificity and sensitivity Safe, rapid, easy, relatively inexpensive Acceptable to providers and to population</td>
<td>Adequate capacity for reporting, follow-up, and treatment of positive screens Cost effective Sustainable program Clear policy guidelines</td>
</tr>
</tbody>
</table>

Tertiary Prevention
• treatment and rehabilitation of disease after it has been diagnosed so as to prevent progression and permanent disability (e.g. HbA1c, eye, and foot monitoring for diabetes)
### Health Promotion Strategies

#### Table 3. Disease Prevention vs. Health Promotion Approach

<table>
<thead>
<tr>
<th>Disease Prevention</th>
<th>Health Promotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health = absence of disease</td>
<td>Health = positive and multidimensional concept</td>
</tr>
<tr>
<td>Medical model (passive role)</td>
<td>Participatory model of health</td>
</tr>
<tr>
<td>Aimed mainly at high-risk groups in the population</td>
<td>Aimed at the population in its total environment</td>
</tr>
<tr>
<td>One-shot strategy, aimed at a specific pathology</td>
<td>Diverse and complementary strategies aimed at a network of issues/determinants</td>
</tr>
<tr>
<td>Directive and persuasive strategies enforced in target groups</td>
<td>Facilitating and enabling approaches by incentives offered to the population</td>
</tr>
<tr>
<td>Focused mostly on individuals and groups of subjects</td>
<td>Focused on a person's health status and environment</td>
</tr>
<tr>
<td>Led by professional groups from health disciplines</td>
<td>Led by non-professional organizations, civic groups, local, municipal, regional, and national governments</td>
</tr>
</tbody>
</table>


**Healthy Public Policy**
- characterized by an explicit concern for health and equity in all areas of policy and by an accountability for health impact
- main aim: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- government sectors must take into account health as an essential factor when formulating policy and should be accountable for the health consequences of their policy decisions
- methods
  - fiscal: imposing additional costs (e.g. taxes on tobacco and alcohol)
  - legislative: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  - social: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)

**Behavior Change**
- health education serves to
  - increase knowledge and skills
  - encourage positive behavior changes and discourage unhealthy choices
- health education is an important component of eliciting behavior change
- behavior is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community
- Health Belief Model (1975)
  - behaviors undertaken by individuals in order to remain healthy are a function of a set of interacting beliefs
  - beliefs include an individual's perception of his or her susceptibility to a disease, the severity of the disease, and the benefits and costs of health-related actions
  - beliefs are modified by socio-demographic and psychosocial variables
  - individuals must believe that the action will have positive consequences
  - individuals must be in a state of readiness
  - behavior can be stimulated by cues to action, which are specific events that can encourage preventive health decisions and actions (e.g. physician recommendation, public advertising)

#### Stages of Change Model
- provides a framework in which the Health Belief Model is applied to facilitating behavior change (e.g. quitting smoking)
**Risk Reduction Strategies**

- **Risk reduction**: lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer).
- **Harm reduction**: tolerance of some degree of risk behavior, while aiming to minimize the adverse outcomes associated with these behaviors (e.g. needle exchange programs).

**Measurements of Health and Disease**

**Life Expectancy**
- The expected number of years that an individual will live based on standardized death rates for the population.
- Usually qualified by country, gender, and age.

**Crude Death Rate**
- Mortality rate from all causes of death per 1,000 in the population.

**Age Standardized Rate**
- Adjustment of the crude rate of a health-related event using a “standard” population.
- Standard population is one with a known number of persons in each age and sex group.
- Standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time).

**Standardized Mortality Rate**
- The ratio of the observed (actual) number of deaths to the expected number of deaths for a group (e.g. age, race, gender, etc.).
- Useful for comparing populations that are significantly different in some aspect (e.g. the causes of death in more and less developed countries).

**Infant Mortality Rate (IMR)**
- Number of deaths among children under 1 yr of age reported during a given time period divided by the number of live births reported during the same time period and expressed per 1,000 live births per year.

**Maternal Mortality Rate (MMR)**
- Number of deaths of women during pregnancy and due to puerperal causes per 100,000 live births per year.

**Proportional Mortality Ratio (PMR)**
- Proportion of all deaths in a specified population over a given period of time attributable to a specific cause.
  - Each cause is expressed as a percentage of all deaths, with the sum of all causes adding to 100%.

**Potential Years of Life Lost (PYLL)**
- Calculated for a population using the difference between the actual age at death and a standard/expected age at death.
- Increased weighting of mortality at a younger age.
Disability Adjusted Life Year (DALY)
- A quantitative indicator of the burden of diseases that reflects the total amount of disability-free life years lost.
- Includes loss from premature mortality and loss due to a degree of disability over a specific period of time; these disabilities can be physical or mental.

Quality Adjusted Life Year (QALY)
- A value from 0 to 1 assigned to a year of life based on perceived quality of life; a year in "perfect" health is considered equal to 1 QALY, the value of a year in ill health would be lowered based on the burden of disease.
- It is possible to have "states worse than death" for example QALY < 0 for extremely serious conditions.

Epidemiology

Population
- A collection of individuals who share a common trait (most commonly applied to a geographic area but it could be another factor such as ethnic group).

Sample
- A selection of individuals from a population or set of observations.
  - Types:
    - Random: all are equally likely to be selected.
    - Systematic: an algorithm is used to select a subset.
    - Stratified: separate representations of more than one subgroup.
    - Cluster: grouped in space/time to reduce costs.
    - Convenience: non-random inclusion, usually volunteers.

Sample Size
- Sample size contributes to the statistical precision of the observed estimate.
- Increasing the sample size decreases the probability of type I and type II errors.

Bias
- Non-random error leading to a deviation of inferences or results from the truth.
- Any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth.
  - Lead-time: time between early diagnosis with screening, and when diagnosis would have been made without screening.
  - Lead-time bias: over-estimation of survival when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening.
  - Incidence-prevalence bias: when prevalent cases include long-term survivors who have a better prognosis than some incident cases.
  - Length-time bias: overestimation of the survival time due to the sampling of prevalent as opposed to incident cases.
  - Sampling bias: occurs with the selection of a sample that does not truly represent the population.
  - Sampling procedures should be chosen to prevent or minimize bias.
  - Recall bias: when individuals with a disease are more prone to recalling or believing they were exposed to a possible causal factor than those who are free of disease.

Confounder
- A variable that is related to both the exposure and outcome but is not measured or is not distributed equally between groups.
- Distorts the apparent effect of an exposure or risk because it may not be possible to separate/ control for the contribution of a single causal factor to an effect (e.g. late maternal age could be a confounder in an investigation of birth order > 4 and risk of developing Trisomy 21).
Prevalence
- total number of cases in a population over a defined period of time
- two forms of prevalence
  - point prevalence: attempts to measure the frequency of all disease at one specific point in time, therefore knowledge of the time of onset of disease is not required
  - period prevalence: measure constructed from prevalence at a point in time, plus new cases and recurrences over a defined period of time
- depends on incidence rate and disease duration from onset to termination (cure or death)
- favors the inclusion of chronic over acute cases and may be used to present a biased picture of the disease
- prevalence studies are cross-sectional and cannot be used for causal inferences
- prevalence figures are useful for determining the extent of a disease and can aid in the rational planning of facilities and services

Sensitivity
- proportion of people with disease who are correctly identified by having a positive test

Specificity
- proportion of people without disease who are correctly identified by having a negative test

Pre-Test Probability
- an estimate of the likelihood a particular patient has a given disease based on known factors

Post-Test Probability
- a revision of the probability of disease after a patient has been interviewed and examined
- calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests, and Bayes' theorem
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
- after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

Figure 4. Understanding sensitivity and specificity

Figure 4a. Hypothetical population

Figure 4b. Results of diagnostic test on hypothetical population

Figure 4c. Sensitivity of test (e.g. 24/30 = 80% sensitive)

Figure 4d. Specificity of test (e.g. 56/70 = 80% specific)

Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain. BMJ 2003;327:716-719

Sensitivity and specificity are characteristics of the test
LR depends on the test characteristics, not the prevalence
PPV and NPV depend on the prevalence of the disease in the population

SPIN: use a Specific test to rule IN a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive.
SNOUT: use a Sensitive test to rule OUT a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative.
TP = True positive  TN = True negative  FP = False positive  FN = False negative

<table>
<thead>
<tr>
<th>Disease</th>
<th>Present</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Result</td>
<td>TP</td>
<td>FP</td>
</tr>
</tbody>
</table>

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

Likelihood Ratio (LR)
- Likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
- LR+ indicates how much the probability of disease increases if the test is positive
- LR- indicates how much the probability of disease decreases if the test is negative

\[
LR+ = \frac{TP}{TP+FN} \quad LR- = \frac{FN}{TP+FN}
\]

Positive Predictive Value (PPV)
- Proportion of people with a positive test who have the disease

\[
PPV = \frac{TP}{TP+FP}
\]

Negative Predictive Value (NPV)
- Proportion of people with a negative test who are free of disease

\[
NPV = \frac{TN}{TN+FN}
\]

Pre-Test Probability
- An estimate of the likelihood a particular patient has a given disease based on known factors such as clinical assessment prevalence of disease in the population. Together with a post-test probability this can be used to interpret a diagnostic test or a series of tests

\[
Pre-Test Odds = \frac{Pr\, prevalence}{1-Pr\, prevalence}
\]

Post-Test Probability
- A revision of the probability of disease after a patient has been examined or a diagnostic test has been conducted
- Calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests and Bayes’ theorem
- The post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
- After each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

\[
Post-Test Odds = Pre-Test Odds \times LR
\]

Post-Test Probability = \frac{Post-test odds}{Post-test odds + 1}

Intention-To-Treat (ITT)
- A strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the requirements of that group
- This is to limit the bias introduced by issues of compliance and to simulate real world situations in which not all patients/providers adhere to the study allocation protocol

Relative Risk (RR)
- Ratio of the incidence of a health outcome among the exposed population to the incidence of the health outcome in the non-exposed population

\[
Relative\, Risk (RR) = \frac{PPV}{1 - NPV} = \frac{TP/(TP+FP)}{FN/(TN+FP)}
\]

Attributable Risk (AR)
- Rate of a health outcome attributable to a hypothetical risk factor for that outcome
- [incidence in exposed population] - [incidence in non-exposed]
- Attributable risk assumes causation

\[
Attributable\, Risk = PPV \times (1 - NPV) = \frac{TP/(TP+FP)}{FN/(TN+FP)}
\]

Advanced Neoplasia

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>68</td>
<td>147</td>
</tr>
<tr>
<td>Negative</td>
<td>216</td>
<td>2234</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>2381</td>
</tr>
</tbody>
</table>

Sensitivity = 68/284 = 23.9%
Specificity = 2234/2381 = 93.8%

Odds Ratio (OR)
- Statistic based on the ratio of two odds, used for estimating the strength of association of a factor
- Statistically significant OR above 1.0 indicates an elevated risk among those exposed beyond chance
- Statistically significant OR lower than 1.0 indicates that the exposure may be protective beyond chance

\[
LR+ = \frac{0.239}{1 - 0.938} = 3.85
\]

\[
LR- = \frac{1 - 0.239}{0.938} = 0.81
\]

\[
PPV = \frac{68}{(68+147)} = 0.316
\]

\[
NPV = \frac{2234}{(2234+216)} = 0.912
\]

Figure 6. Clinical epidemiology definitions and practical example using FOBT testing in advanced colon cancer
**Effectiveness of Interventions**

**DEFINITIONS**

**Relative Risk Reduction (RRR)**
- proportional reduction in rates of adverse outcomes between experimental and control participants in a trial

**Absolute Risk Reduction (ARR)**
- absolute arithmetic difference in rates of adverse outcomes between experimental and control participants in a trial
- it is hypothesized that events will occur more often in control group than in experimental group where the intervention is protective (e.g. a vaccine)

**Absolute Risk Increase (ARI)**
- absolute arithmetic difference in rates of adverse outcomes between control and experimental participants in a trial
- it is hypothesized that events will occur more often in experimental group than in control group when the intervention is harmful (e.g. alcohol excess)

**Number Needed to Treat (NNT)**
- number of patients who need to be treated to achieve one additional favorable outcome
- only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility of intervention)
- a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

**Number Needed to Harm (NNH)**
- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

**Adherence (Formerly Compliance)**
- degree to which a patient follows a treatment plan

**Effectiveness, Efficacy, Efficiency**
- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - **efficacy**: the extent to which a specific intervention produces a beneficial result under ideal conditions
  - ideally, based on the results of a randomized control trial (the theoretical impact)
  - **effectiveness**: measures the benefit of an intervention under usual conditions of clinical care
  - considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
  - **efficiency**: a measure of economy of an intervention with known effectiveness
  - considers the optimal use of resources (e.g. money, time, personnel, equipment, etc.)

**Types of Study Design**

**Qualitative vs. Quantitative**

<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Quantitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generates hypothesis (Why? What does it mean?)</td>
<td>Tests hypothesis (What? How much/many?)</td>
</tr>
<tr>
<td>Inductive (specific to general): “bottom up”</td>
<td>Deductive (general to specific): “top down”</td>
</tr>
<tr>
<td>Observation → pattern → tentative hypothesis → theory</td>
<td>Theory → hypothesis → observation → confirmation</td>
</tr>
<tr>
<td>Sampling approach to obtain representative coverage of ideas or concepts</td>
<td>Sampling approach to obtain representative coverage of people in the population</td>
</tr>
<tr>
<td>Narrative: rich, contextual, and detailed information from a small number of participants</td>
<td>Numeric: frequency, severity, and associations from a large number of participants</td>
</tr>
</tbody>
</table>

Source: Adapted from http://phprimer.afmc.ca
### Quantitative Research Methods

**Figure 7. Quantitative study designs**

Source: Adapted from http://phprimer.afmc.ca

### Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study subjects
- there are two main subtypes of observational studies: descriptive and analytic studies

#### Descriptive Studies
- describe the events and rates of disease with respect to person, place and time and to estimate disease frequency and time trends
- first sets of studies and are used to generate an etiologic hypothesis, not test a hypothesis

#### Analytic Studies
- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

**Table 5. Observational Study Designs**

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Ecological</th>
<th>Cross-Sectional</th>
<th>Case-Control (Figure 8)</th>
<th>Cohort (Figure 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Units of analysis are populations or groups of people, rather than individuals</td>
<td>Assessment of individuals with respect to presence and absence of exposures and diseases at the same point in time</td>
<td>Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)</td>
<td>Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>Population (e.g. geographic areas)</td>
<td>Population (sample)</td>
<td>Two study sample populations are compared: cases and controls</td>
<td>One or more cohorts Cohort: group of people with common characteristics (e.g. year of birth) Divided into measured exposed vs. non-exposed groups</td>
</tr>
</tbody>
</table>

**Formulating a Research Question**

- **PICO**
  - **P**atient Characteristics
  - **I**ntervention of Interest
  - **C**omparison Group or Control Group
  - **O**utcome that you are trying to prevent or achieve
**Table 5. Observational Study Designs (continued)**

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Ecological</th>
<th>Cross-Sectional</th>
<th>Case-Control (Figure 8)</th>
<th>Cohort (Figure 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Descriptions of the average exposure or risk of disease for a population</td>
<td>Collect information from each person at one particular time</td>
<td>Ask cases and controls about exposures</td>
<td>Subjects are followed for a specific period of time to determine development of disease in each exposure group</td>
</tr>
<tr>
<td></td>
<td>Tabulate the numbers in groups (e.g. by presence or absence of disease/factor of interest)</td>
<td>Tabulate the number of persons at a particular point in time</td>
<td>Select all the cases of a specific disease during a specific time frame</td>
<td>Prospective: measuring from the exposure to the future outcomes – looking forward</td>
</tr>
<tr>
<td></td>
<td>Make 2 x 2 table and compare groups</td>
<td>Identify variables</td>
<td>Represent the general population</td>
<td>Retrospective: measuring from outcomes to possible risk factors or protective factors – looking back</td>
</tr>
<tr>
<td></td>
<td>Estimate prevalence</td>
<td>Estimate incidence</td>
<td>To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender)</td>
<td>Collect information on factors from all persons at the beginning of the study</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Quick, easy to do</td>
<td>Determines association between variables</td>
<td>Used when disease in population is rare (less than 10% of population) due to increased efficiency</td>
<td>Shows an association between a factor and an outcome/ several outcomes</td>
</tr>
<tr>
<td></td>
<td>Uses readily available data</td>
<td>Quick and uses limited resources</td>
<td>Less costly and time consuming</td>
<td>Stronger evidence for causation</td>
</tr>
<tr>
<td></td>
<td>Generates hypothesis</td>
<td>Surveys with validated questions allows comparison between studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Poor generalizability to individual level (not direct assessment of causal relationship)</td>
<td>Does not allow for assessment of temporal relationship or causation between variables</td>
<td>Recall bias (see PH7)</td>
<td>By itself, cannot establish causation</td>
</tr>
<tr>
<td></td>
<td>Ecological fallacy: an incorrect inference about individuals in the population</td>
<td>Recall bias (see PH7)</td>
<td>Confounding bias for controls</td>
<td>Confounding factors are common as the cohort self-selects the exposure, or unknown/unmeasured factors are associated with the measured exposure</td>
</tr>
<tr>
<td></td>
<td>Exposed group Unexposed group</td>
<td>Only one outcome can be measured</td>
<td>Only one outcome can be measured</td>
<td>Cost and duration of time needed to follow cohort</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>A study looking at the association between smoking rates and lung cancer rates in different countries at the population level without individual data on both factors</td>
<td>A study that examines the distribution of BMI by age in New York at a particular point in time</td>
<td>A famous case control study is by Sir Richard Doll who demonstrated the link between tobacco smoking exposure and lung cancer cases at the individual level</td>
<td>A famous cohort study is the Framingham Heart Study, which assessed the long-term cardiovascular risks of diet, exercise, medications such as ASA, etc.</td>
</tr>
</tbody>
</table>

---

**Experimental Study Designs**

- not discussed here are non-randomized control trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible) and clinical trials (test treatments or laboratory tests in human subjects)

**RANDOMIZED CONTROLLED TRIAL (RCT)**

**Definition**

- subjects are assigned by random allocation to two or more groups, one of which is the control group, the other group(s) receive(s) an experimental intervention

**Subjects**

- individuals are separated into groups by a random process to ensure as much as possible equal distribution of known and unknown factors except for the experimental exposure (e.g. the treatment)
Methods

- random allocation of individuals into two or more treatment groups through a centralized concealed process
- method of assessment to reduce bias
  - single-blind: subject does not know group assignment (intervention or placebo)
  - double-blind: subject and observer both unaware of group assignment
  - triple-blind: subject, observer, and analyst unaware of group assignment (rarely done)
- one group receives placebo or standard therapy
- one or more groups receive(s) the intervention(s) under study
- the outcome is measured and the groups are compared
- all other conditions are kept the same between groups

Advantages

- “gold standard” of studies, upon which the practice of EBM is founded
- provides the strongest evidence for effectiveness of intervention
- with sufficient sample size and appropriate randomization, threats to validity are minimized
- allows prospective assessment of the effects of intervention while minimizing bias

Disadvantages

- some exposures are not amenable to randomization (e.g. cannot randomize subjects to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
- difficult to randomly allocate groups (e.g. communities, neighbourhoods)
- difficult to study rare events, since RCTs would require extremely large sample sizes
- costly

Methods of Analysis

Distributions

- distribution describes the probability of events
- normal (Gaussian) or non-normal (skewed, bimodal, etc.)
- characteristics of the normal distribution
  - mean = median = mode
  - 67% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - mean: sum of all observations divided by total number of variables
  - median: value at the 50th percentile, this is a better reflection of the central tendency for a skewed distribution
  - mode: most frequently observed value in a series
- measures of dispersion
  - range: the largest value minus the smallest value
  - variance: a measure of the spread of data
  - standard deviation: the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

Data Analysis

Statistical Hypotheses

- null (H₀)
  - no relationship exists between the two stated variables (i.e. no association between the hypothesized exposure and the outcome)
- alternative (H₁)
  - a relationship does exist between the two stated variables

Type I Error (α Error)

- the null hypothesis is falsely rejected (i.e. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error, since a type I error can have larger clinical significance than a type II error

Type II Error (β Error)

- the null hypothesis is falsely accepted (i.e. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
• higher level of error is acceptable for most studies
  • can also be used to calculate statistical power

Power
• probability of correctly rejecting a null hypothesis when it is in fact false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
  • power increases with an increase in sample size
  • power = 1 – β, and is therefore equal to the probability of a true positive result

Statistical Significance
• the probability that the statistical association found between the variables is due to random chance alone (i.e. that there is no association)
  • the preset probability is set sufficiently low that one would act on the result; frequently p=0.05
  • when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (i.e. p<0.05)

Clinical Significance
• measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
  • depends on factors such as cost, availability, patient compliance, and side effects in addition to statistical significance

Trend
• an observed directional relationship that does not meet criteria for statistical significance and thus should be interpreted with caution

Confidence Interval (CI)
• provides a range of values within which the true population result (e.g. the mean) lies
  • frequently reported as 95% CI (i.e. one can be 95% certain that the true value is within this data range)
  • bounded by the upper and lower confidence limits

Data
• information collected from a sample of a population
  • there are 2 overall classes of data listed with examples
    • discrete
      • categorical (e.g. gender, marital status)
      • ordinal (e.g. low, medium, high)
    • continuous (e.g. serum cholesterol, hemoglobin, age)

Accuracy
• how closely a measurement approaches the true value

Reliability
• how consistent a measurement is when performed by different observers under the same conditions or by the same observer under different conditions

Validity
• extent to which a measurement approaches what it is designed to measure
  • determined by the accuracy and reliability of a test

Internal Validity
• degree to which the findings of the sample truly represent the findings in the study population
  • dependent on the precision and accuracy

External Validity
• degree to which the results of the study can be generalized to other situations or populations
## Common Statistical Tests

### Table 6. Statistical Tests

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Z-Test (known as T-Test for samples &lt;30)</th>
<th>Analysis of Variance (ANOVA)</th>
<th>Chi-Squared Test ($\chi^2$)</th>
<th>Linear Regression</th>
<th>Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>What are you trying to show?</td>
<td>Compare the mean values of an outcome variable between two groups (e.g. difference in average BP between men and women)</td>
<td>Compare the mean values of an outcome variable between two or more groups (e.g. difference in average BP between persons in three towns)</td>
<td>Test the correspondence between a theoretical frequency distribution and an observed frequency distribution (e.g. if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test determines if this variation is more than expected due to chance alone)</td>
<td>Looks at associations between two or more continuous variables (e.g. age and blood pressure)</td>
<td>Shows how a change in one explanatory variable affects the status (e.g. ill vs. non-ill) of the outcome variable</td>
</tr>
<tr>
<td>What kind of data do you have in your study?</td>
<td>Data on two groups</td>
<td>Mean of groups (one or more) Overall mean of an entire sample</td>
<td>Data on two or more populations and two or more outcome measures</td>
<td>Data on at least one population</td>
<td>Data on at least one population</td>
</tr>
<tr>
<td>What kind of variables do you measure?</td>
<td>Continuous data</td>
<td>Continuous data</td>
<td>Categorical (2 or more)</td>
<td>Continuous</td>
<td>Categorical (discrete outcomes usually dichotomous)</td>
</tr>
<tr>
<td>Dependent Variable</td>
<td>Categorical (2 only)</td>
<td>Categorical (2 or more)</td>
<td>Categorical (2 or more)</td>
<td>Continuous</td>
<td>Continuous/categorical</td>
</tr>
<tr>
<td>Independent Variable</td>
<td>Continuous data</td>
<td>None</td>
<td>None</td>
<td>Independent variable has &quot;normal&quot; distribution</td>
<td>None</td>
</tr>
<tr>
<td>Assumptions</td>
<td>&quot;Normal&quot; distribution</td>
<td>None</td>
<td>Linear relationship between variables</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

## Causation

### Criteria for Causation (Sir Bradford Hill)

1. **strength of association**: the frequency with which the factor is found in the disease and the frequency with which it occurs in the absence of disease
2. **consistency**: is it the same outcome with different populations or study design?
3. **specificity**: is the association particular to your intervention and measured outcome?
4. **temporal relationship**: did the exposure occur before the onset of the disease?
5. **biological gradient**: finding a quantitative relationship between the factor and the frequency (e.g. dose response relationship)
6. **biological plausibility**: does the association/ causation make biological sense?
7. **coherence**: can the relationship be explained/accounted for based on what we know about the laws of science, logic, etc.?
8. **experimental evidence**: experiment that investigates what happens when the suspected offending agent is removed (e.g. is there improvement?)
9. **analogy**: do other established associations provide a model for this type of the relationship?

### Assessing Evidence

- critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision
A. Are the results of the study valid?
- see below for classifications of evidence that has already been assessed; see sidebar for assessing primary studies

B. What are the results?
- what was the impact of the treatment effect?
- how precise was the estimate of treatment effect?
- what were the confidence intervals and power of the study?

C. Will the results help me in caring for my patients?
- are the results clinically significant?
- can I apply the results to my patient population?
- were all clinically important outcomes considered?
- are the likely treatment benefits worth the potential harm and costs?

Levels of Evidence: Classifications Cited in Guidelines/Consensus Statements

- Level I evidence: based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results
- Level II evidence: based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results
- Level III evidence: based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies
- Level IV evidence: based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines
- Level V evidence: opinions of the individuals who have written/reviewed the guidelines (i.e. Level IV evidence), based on experience/knowledge of literature/peer discussion

Notes: These 5 levels of evidence are not direct evaluations of evidence quality or credibility; they reflect the nature of the evidence. While RCTs tend to be most credible (with <III), Level III evidence gains credibility when multiple studies from different locations and/or time periods report consistent findings. Level IV and V evidence reflects decision-making that is necessary but in the absence of published evidence.

Figure 12. Pyramid of pre-appraised evidence
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Figure 13. Levels of evidence classifications
Note: this is only one method of classifying evidence. Various systems exist, but operate within the same premise that certain types of evidence carry more weight than others

META-ANALYSIS

Definition
- a form of statistical analysis that combines the results of independent studies addressing a common research hypothesis, as identified through systematic review, into one large study

Subjects
- combination of all the subjects used in original studies

Methods
- selection of relevant studies from the published literature which meet quality criteria
- statistical models used to combine the results of each independent study
- provides a summary statistic of overall results as well as graphic representation of included studies
Advantages
- attempts to overcome the problem of reduced power due to small sample sizes of individual studies
- ability to control for inter-study variation

Disadvantages
- sources of bias may not be controlled for
- reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)
- the decision to include/reject a particular study is subjective

Health Services Research

Continuous Quality Improvement

Quality Improvement
- method of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to be the cause of variation in quality, as opposed to individuals
- taking measures to increase efficiency of action with the purpose of achieving optimal quality

Quality Assurance
- management system to assure the quality of health care provided by workers and received by patients
- constantly aims to improve standards and the frequency of attaining those standards
- five-stage process of quality assurance
  1. establishment of functional goals
  2. implementation of procedures to achieve those goals
  3. regular assessment of performance relative to the goals
  4. proposal of solutions to close the gap between performance and goals
  5. documentation and reporting of this assessment activity

Quality Control
- method of maintaining standards by reviewing the quality of all factors involved in the process

Continuous Quality Improvement
- management approach to improve and maintain quality via continuous assessment of potential defects, followed by action to improve process, avoid decrease in quality or correcting process in early stages
- continuous feed-forward process

Quality Management
- encompasses quality assurance, quality control, and quality improvement to achieve consistent quality

Total Quality Management
- management philosophy for improving quality while controlling costs
- focusing on the system rather than the individual, to ensure decisions are made to support quality and remove barriers to quality inherent in bureaucratic, hierarchical systems

Audit
- process of systematic examination of a quality system carried out by internal or external quality auditors
- to determine whether quality processes and results comply with goals, and whether processes have been implemented effectively

Systems Analyses Tools
1. 5 Whys: brainstorming to simplify the process of change; continue asking ‘why’ until the root of the problem is discovered
2. Ishikawa Diagrams (i.e. Fishbone Diagrams): identify generic categories of problems that have an overall contribution on the effect

An example of a meta-analysis is one that includes the full set of reported studies based on compiling and analyzing data from eligible RCTs, which compare the effects of ACEI, CCBs, and other antihypertensive agents on mortality and major cardiovascular events.
3. **Defect check sheets:** consider all defects and tally up the number of times the defect occurs

4. **Pareto Chart:** x vs. y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis
   - purpose is to highlight most important among large set of factors contributing to defects/poor quality

**Precede-Proceed Model**
- tool for designing, implementing, and evaluating health interventions/programs

<table>
<thead>
<tr>
<th>PRECEDE Phase</th>
<th>PROCEED Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 – Identify the ultimate desired result</td>
<td>Phase 5 – Implementation (design and conduct the intervention)</td>
</tr>
<tr>
<td>Phase 2 – Identify and set priorities among health issues and their behavioural and environmental determinants</td>
<td>Phase 6 – Process Evaluation (determine if the program is implemented as planned)</td>
</tr>
<tr>
<td>Phase 3 – Identify the predisposing, enabling, and reinforcing factors that affect the behaviors and environmental determinants</td>
<td>Phase 7 – Impact Evaluation (measure intermediate objectives – predisposing, enabling, and reinforcing factors)</td>
</tr>
<tr>
<td>Phase 4 – Identify the administrative and policy factors that influence what can be implemented</td>
<td>Phase 8 – Outcome Evaluation (measure desired result)</td>
</tr>
</tbody>
</table>

**Cost Analysis**

**Cost-Benefit Analysis (CBA)**
- a process of, either explicitly or implicitly, weighing the total expected costs against the total expected benefits of one or more actions in order to choose the best or most profitable option
- all costs are adjusted for the time value of money so that costs that may change over time are expressed on a common basis in terms of their present value

**Cost Effectiveness Analysis (CEA)**
- a comparison of the relative expenditure (costs) and outcomes (effects) of two or more courses of action
- cost effectiveness analysis is often used where a full cost benefit analysis is inappropriate
- a CEA is commonly expressed in terms of a ratio: the denominator is a gain in health from a measure (e.g., years of life, premature births averted, sight-years gained) and the numerator is the cost of the health gain
- the most commonly used outcome measure is quality-adjusted life years (QALY), see PH7

**Outbreak of Infectious Diseases**

**Definitions**

**Outbreak**
- occurrence of new cases clearly in excess of the baseline frequency of the disease in a defined community or population over a given period of time
- synonymous with epidemic, although generally considered to be an epidemic that is localized, has an acute onset, or is relatively short in duration
Epidemic
- any disease, infectious or chronic, occurring at a greater frequency than usually expected in a defined community or institutional population over a given time period (i.e. excessive rate of disease)

Endemic
- constant presence of disease or infectious agent in a given geographic area or population subgroup (i.e. usual rate of disease)

Pandemic
- epidemic over a wide area, crossing international boundaries, and affecting a large number of people

Attack Rate
- cumulative incidence of infection within a defined group observed during a specific period of time in an epidemic
- calculated by dividing the total number of people who develop clinical disease by the population at risk, usually expressed as a percentage

Secondary Attack Rate
- number of cases among contacts occurring within the incubation period following exposure to the primary case, in relation to the total exposed contacts
- infectiousness reflects the ease of disease transmission and is usually measured by the secondary attack rate

Pathogenicity Rate
- power of an organism to produce clinical disease in those that are affected

Virulence
- severity of the disease produced by the organism in a given host
- expressed as the ratio of the number of cases of severe and fatal infection to the total number of clinically affected

Case-Fatality Rate
- proportion of individuals contracting a disease who die as a result of that disease
- most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths
- must be clearly differentiated from the mortality rate

Mortality Rate/Crude Death Rate
- estimation of the portion of the population that dies during a specified period from all causes of death

All-Cause Mortality Rate by Age Group
- estimation of the portion of the population in a given age group that dies during a specified period from all causes of death for that age group

Morbidity Rate
- estimation of the portion of the population that suffers illness or ill health during a specified period

Steps to Control an Outbreak
1. Define the Problem
   - is it an outbreak?

2. Appraise Existing Data and Institute a Surveillance System
   - case definition: formulated from the most common symptoms or signs; definition includes the likely date of onset of illness of the first case (e.g. any person with onset of fever higher than 101.3°F and cough within past 28 d)
   - active surveillance: identify those who may have been exposed to the infectious agent and who fit the case definition through active efforts, including:
     - contacting emergency rooms, physicians’ offices, local schools
     - obtaining records from health units, such as mortality or laboratory records

3. Formulate Hypotheses and Implement Initial Control Measures
   - track outbreak evolution to develop hypotheses about potential source and populations at risk
   - case management depends on symptoms, suspected agent, population at risk, and location

Infection Control Precautions
(see Infectious Diseases, ID6)
- Contact (impetigo, chicken pox, warts)
  - Wash hands
  - Gloves
  - Gown
  - Wipe equipment after use

Airborne (TB)
- Contact precautions PLUS
  - N95 mask (fit tested)
  - Negative pressure room

Droplet (influenza, mumps, pneumonia)
- Contact precautions PLUS
  - Goggles/face shield
  - Surgical mask


Active Surveillance
Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection)

Passive Surveillance
A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered)
• population management requires public health services in the community and infection control teams in hospitals to disseminate information about
  ▪ risk reduction
  ▪ personal preventative measures (e.g. post-exposure prophylaxis)
  ▪ decreasing risk of propagation (e.g. quarantine)

4. Test the Hypothesis through Analysis of Surveillance Data or Special Studies
• analyze outbreak surveillance data
• generate epidemic curves
  ▪ usually a frequency histogram, with the number of cases plotted on the vertical axis and dates or times of onset along the horizontal axis
  ▪ curve can indicate whether the epidemic (outbreak) has a common source or whether it is propagated
  ▪ point source epidemic: exposure is brief and essentially simultaneous
  ▪ extended source epidemic: exposure lasts for a period of days to weeks and may be continuous (no irregular peaks) or intermittent (irregularly spaced peaks)
  ▪ propagated epidemic: begins with only a few exposed persons but is maintained by person-to-person transmission (e.g. measles/influenza); epidemic curve shows a series of peaks
• use epidemic curves, cross-sectional studies, and/or case-control studies to evaluate hypotheses about cause of outbreak

5. Draw Conclusions and Re-Adjust Hypothesis and Control Measures
• establish cause of outbreak with further epidemiologic investigation and revise initial control measures accordingly

6. Plan for Long-Term Prevention and Control
• implement prevention measures to avoid similar future incidents
  ▪ strengthen resistance of hosts (e.g. immunization)
  ▪ interrupt modes of transmission in environment (e.g. improvements in food processing)
• communicate outbreak prevention and control strategies to the public

Environmental Health

Definition
• study of conditions in the natural and human-made environment that influence human health and well-being
• environmental exposures
  ▪ four main reservoirs: air, food, water, and soil
  ▪ three main routes: inhalation, ingestion, or absorption (skin)
  ▪ usually divided into two main settings
    ▪ workplace (including schools): may see high level exposure in healthy individuals (see Occupational Health, PH23)
    ▪ non-workplace: generally low level but chronic exposure; population at risk includes extremes of age, developing fetuses, and ill or immunocompromised individuals
• health impacts of the environment also include factors such as urban planning and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths are neighborhood features that can facilitate more active lifestyles among residents)

Environmental Health Jurisdiction

<table>
<thead>
<tr>
<th>Public Health Unit</th>
<th>Enforcement of water and food safety regulations (including restaurant food safety)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sanitation</td>
</tr>
<tr>
<td></td>
<td>Assessment of local environmental risks</td>
</tr>
<tr>
<td></td>
<td>Monitoring and follow-up of reportable diseases</td>
</tr>
<tr>
<td>Municipal Government</td>
<td>Waste disposal</td>
</tr>
<tr>
<td></td>
<td>Recycling</td>
</tr>
<tr>
<td></td>
<td>Water and sewage treatment/collection/distribution</td>
</tr>
<tr>
<td>State Government</td>
<td>Water and air quality standards</td>
</tr>
<tr>
<td></td>
<td>Industrial emission regulation</td>
</tr>
<tr>
<td></td>
<td>Toxic waste disposal</td>
</tr>
<tr>
<td>Federal Government</td>
<td>Designating and regulating toxic substances</td>
</tr>
<tr>
<td></td>
<td>Regulating food products</td>
</tr>
<tr>
<td></td>
<td>Setting policy for pollutants that can travel across provincial boundaries</td>
</tr>
<tr>
<td>International</td>
<td>Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change,</td>
</tr>
<tr>
<td></td>
<td>International Joint Commission)</td>
</tr>
</tbody>
</table>
Risk Assessment

Hazard Identification
• what is the hazard involved?
• assess potential hazards by taking an environmental health history

Risk Characterization
• is the identified agent likely to elicit the patient’s current symptoms?
• review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. evaluate threshold levels)

Exposure Assessment
• is the patient’s exposure to the environmental agent sufficient to have caused the current symptoms?
• quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard

Air

Physical Contaminants
• sound waves
  ▪ ionizing radiation
  ▪ radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with a small proportion of lung cancers
• ultraviolet radiation is increasing due to ozone layer destruction and increases risk of skin cancer
  ▪ non-ionizing radiation
  ▪ visible light, infrared, microwave

Chemical Contaminants
• ground-level ozone
  ▪ main component of smog with levels increasing in major cities
  ▪ worsens asthma, irritates upper airway
• carbon monoxide (fossil fuel-related, common byproduct of combustion)
  ▪ aggravates cardiac disease at low levels
  ▪ headache, nausea, dizziness at moderate levels
  ▪ fatal at high levels
• sulphur dioxide (fossil fuel-related), nitrogen oxides
  ▪ contribute to acid rain and exacerbate breathing difficulties
• organic compounds at high levels (e.g. benzene, methylene chloride, tetrachloroethylene)
  ▪ tend to be fat-soluble, easily absorbed through skin and difficult to excrete
• heavy metals emissions (e.g. nickel, cadmium, chromium)
  ▪ variety of health effects: upper airway disease, asthma, decreased lung function
• second-hand tobacco smoke
  ▪ respiratory problems, increase risk of lung cancer
  ▪ particulates associated with decreased lung function, asthma, upper airway irritation

Biological Contaminants
• molds thrive in moist areas; 10-15% of the population allergic
• bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. Legionella)
• dust mites (year-round) and pollens (seasonal) can trigger upper and lower-airway symptoms

Climate Change
• anthropogenic greenhouse gas emissions (e.g. carbon dioxide, methane) leading to adverse changes in the global environment
  ▪ increased extreme weather conditions (e.g. floods, hurricanes, heat waves)
  ▪ increased distribution of disease vectors (e.g. mosquitoes and malaria)
### Water

**Biological Contaminants**
- mostly due to human and animal waste
- rural inhabitants at higher risk
- bacteria: Escherichia coli (e.g. Walkerton, ON), Salmonella, Pseudomonas, Shigella
- protozoa: Giardia, Cryptosporidium (e.g. North Battleford, SK)

**Chemical/Industrial Contaminants**
- chlorination by-products (e.g. chloroform can cause cancer at high levels)
- volatile organic compounds, lead, pesticides, motor oil, other industrial waste products
- health effects:
  - infants and toddlers at highest risk of exposure due to hand-mouth behaviors
  - dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, N/V, fatigue
- biological contamination: tetanus, Pseudomonas

### Soil

- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, residue of industrial waste/development (e.g. urban agriculture), lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- health effects
  - infants and toddlers at highest risk of exposure due to hand-mouth behaviors
  - dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, N/V, fatigue
- biological contamination: tetanus, Pseudomonas

### Food

**Table 9. Comparison of Select Biological Contaminants of Food and Effects on Human Health**

<table>
<thead>
<tr>
<th>Source</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>GI symptoms</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Joint pain, GI symptoms</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Watery or bloody diarrhea, HUS</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Listeriosis: nausea, vomiting, fever, headache, rarely meningitis or encephalitis</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td>Dizziness, weakness, respiratory failure, GI symptoms: thirst, nausea, constipation</td>
</tr>
<tr>
<td>Prion (BSE)</td>
<td>Creutzfeld-Jakob disease</td>
</tr>
</tbody>
</table>

BSE = bovine spongiform encephalopathy

- other biological food contaminants include
  - viruses, mold toxins (e.g. aflatoxin has been associated with liver cancer), parasites (e.g. Toxoplasmosis, tapeworm), paralytic and shellfish poisoning (rare), genetically modified organisms (controversial as to health risks/benefits)

**Chemical Contaminants**

- many persistent organic pollutants are fat-soluble and undergo bioamplification
- drugs (antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrates highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
- pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects
  - polychlorinated biphenyls (PCBs)
  - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
- dioxins and furans
  - levels highest in fish and marine mammals, also present in breast milk
  - can cause immunosuppression, liver disease, respiratory disease

**To Fluoridate or Not**

At the recommended concentration of 0.8-1.0 mg/L, fluoride reduces cavities by 18-40%, and there is little risk of fluorosis unless other exposures (e.g. toothpaste, rinses, mouthwash, etc.) are swallowed. Opposition raises concerns that the intake is not easily controlled, and that children, and others may be more susceptible to health problems. However, public health experts strongly support fluoridation as an effective measure to prevent dental caries at the community level and reduce dental health inequities.

**The Walkerton Tragedy**

In May 2000, the drinking water system in the town of Walkerton, ON, became contaminated with *Escherichia coli* O157:H7 and Campylobacter jejuni. Over 2,300 individuals became ill; 27 people developed hemorrhagic uremic syndrome and 7 individuals died in the outbreak.


**Honey and Botulism**

Although exceedingly rare, infant botulism has been documented as a form of food poisoning from *C. botulinum* found in honey. When an infant swallows spores of this bacterium, they grow and produce a toxin in the baby’s intestine. By the time an infant is 1, its gut has a healthy colony of “good” bacteria that prevents this from occurring.

**Organic Foods**

- Organic foods are not free of synthetic pesticide residues but typically contain smaller amounts compared to conventionally grown foods
- Currently, there has not been strong evidence to suggest that eating organic foods is safer or more nutritious compared to eating conventionally grown food

**Heavy Metal Toxicity**

**Mechanism**
- after exposure, superabundant metals bind to proteins, alter their enzymatic activity, and lead to diffuse disease manifestations

**Predisposing Factors in At-Risk Groups**
- children: hand-to-mouth, incomplete blood-brain barrier
- pregnant women and developing fetus: heavy metals cross placenta; mothers release heavy metal stores at times of calcium stress
- adults: occupation, hobbies, environment (home, country)

**Etiology**
- iatrogenic (e.g. gold treatment for rheumatoid arthritis, lithium treatment for bipolar affective disorder)
- inhalation (e.g. zinc oxide, lead, gasoline fumes)
- ingestion (e.g. lead paint, mercury in fish, folk remedies)
- industry (e.g. methyl mercury industrial spill caused Minamata disease)

**Treatment**
- generalized workup: symptoms are usually wide-ranging and non-specific
- chelation therapy (e.g. dimercaprol)

---

**Occupational Health**

- occupational health is the maintenance and promotion of health in the work environment
- services encompass health promotion and protection (primary prevention), disease prevention (secondary prevention), and treatment and rehabilitation (tertiary prevention)
- general bias towards reporting occupational injuries vs. occupational disease, as occupational disease is harder to identify

---

**Workplace Health Promotion and Protection**

- take action in the workplace so the worker is protected from injury or illness
  - identifying workplace hazards (e.g. through material safety data sheets [MSDS])
  - assessing risk
  - reducing exposure
    - source: substituting a less toxic chemical
    - path: enclosing a source of noise in a sound-proof room
    - worker: personal protection equipment (e.g. reflective vests, helmets)
    - worker education: emergency protocols, material safety education
    - rotation of workers: decrease exposure for each worker but more workers exposed

---

**Workplace Disease Prevention**

- monitor workers’ health to prevent the development of disease
  - periodic examinations to facilitate pre-symptomatic diagnosis (e.g. screening for lead exposure); substance misuse screening where performance impairment is suspected

---

**Workplace Treatment and Rehabilitation**

- treat injury or illness with safe return to the workplace
- may require rehabilitation, retraining, change in job duties, and/or workers’ compensation

---

**Workplace Legislation**

- Department of Labor (DOL) administers and enforces more than 180 federal laws that cover many workplace activities for about 10 million employers and 125 million workers
- the Occupational Safety and Health (OSH) Act is administered by the Occupational Safety and Health Administration (OSHA)
- safety and health conditions in most private and public industries are regulated by OSHA or OSHA-approved state programs
• employers must comply with the General Duty Clause of the OSH Act, which requires employers to keep their workplace free of serious recognized hazards
• compliance duties owed to each employee include the provision of personal protective equipment and training as necessary
• employees retain the right to:
  ▪ ask OSHA to inspect their workplace
  ▪ use their rights under the law without retaliation and discrimination
  ▪ receive information and training about hazards, methods to prevent harm, and the OSHA standards that apply to their workplace. The training must be in a language you can understand
  ▪ get copies of test results done to find hazards in the workplace
  ▪ review records of work-related injuries and illnesses
  ▪ get copies of their medical records
• OSHA enforces the Act through workplace inspections and investigations

Taking an Occupational Health History

• current and previous job duties
• exposures
  ▪ identification: screen for chemical, metal, dust, biological, and physical hazards as well as psychological stressors; review relevant workplace MSDS
  ▪ assessment: duration, concentration, route, exposure controls (e.g. ventilation, personal protective equipment)
• temporal relationship: changes in symptoms in relationship to work environment
• presence of similar symptoms in co-workers
• non-work exposures: home, neighborhood, hobbies

Occupational Hazards

<table>
<thead>
<tr>
<th>Physical</th>
<th>Chemical</th>
<th>Biological</th>
<th>Psychosocial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma (fractures, lacerations)</td>
<td>Organic solvents (e.g. benzene, methyl alcohol)</td>
<td>Exposure to bacteria, viruses, fungi, protozoa, Rickettsia</td>
<td>Workload, responsibility, fear of job loss, geographical isolation, shift work, harassment (sexual/non-sexual)</td>
</tr>
<tr>
<td>Noise (hearing loss)</td>
<td>Noise (hearing loss)</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Temperature (heat cramps, heat exhaustion, heat stroke)</td>
<td>Temperature (heat cramps, heat exhaustion, heat stroke)</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Air pressure (barotrauma, decompression sickness)</td>
<td>Air pressure (barotrauma, decompression sickness)</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Ergonomic</td>
<td>Ergonomic</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Repetitive use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment</td>
<td>Repetitive use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Tendinitis, bursitis, carpal tunnel syndrome</td>
<td>Tendinitis, bursitis, carpal tunnel syndrome</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Radiation</td>
<td>Radiation</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Non-ionizing: visible light, infrared</td>
<td>Non-ionizing: visible light, infrared</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Ionizing: UV, x-rays, γ rays</td>
<td>Ionizing: UV, x-rays, γ rays</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>Electricity</td>
<td>Electricity</td>
<td>Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
</tbody>
</table>

Table 10. Occupational Hazards
Appendix – Reportable Diseases

As an essential part of the health system, physicians are required by law to report certain diseases to public health for the following reasons:

1. to control the outbreak
   - if the disease presents an outbreak threat (e.g. measles, *Salmonella*, respiratory diseases in institutions)
2. to prevent spread
   - if the disease presents a significant threat to individuals or a subset of the population
     (e.g. Lassa Fever)
3. for surveillance
   - if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment and/or partner notification (e.g. gonorrhea, TB)
5. reporting details (website, office, etc.)
   - some are more urgent than others (must contact MOH)
   - physicians should also report unlisted diseases that appear in clusters

The following list is based on the reportable diseases in the province of Ontario, Canada for 2014
(Each state will have its own similar legislation)

Source: Health Protection and Promotion Act, O. Reg. 559/91, amended to O. Reg.49/07.

| Acquired Immunodeficiency Syndrome (AIDS) | Rabies |
| Acute flaccid paralysis <15 yr | Respiratory infection outbreaks in institutions |
| Amoebiasis | Rubella |
| Anthrax | Rubella, congenital syndrome |
| Botulism | Salmonellosis |
| Brucellosis | Severe Acute Respiratory Syndrome (SARS) |
| *Campylobacter* enteritis | Shigellosis |
| Chancroid | Smallpox |
| *Chlamydia trachomatis* infections | Streptococcal infections, Group A |
| Cholera | invasive |
| *Clostridium difficile* associated disease (CDAD) outbreaks in public hospitals | Streptococcal infections, Group B |
| Cyclosporiasis | neonatal |
| Cryptosporidiosis | Syphilis |
| *Cytomegalovirus* infection, congenital | Tetanus |
| Diphtheria | Transmissible spongiform encephalopathy, including:
  i. Creutzfeldt-Jakob disease, all types |
  ii. Gerstmann-Sträussler-Scheinker syndrome |
  iii. Fatal familial insomnia |
  iv. Kuru |
| Encephalitis, including: |
  i. Primary, viral |
  ii. Post-infectious |
  iii. Vaccine-related |
  iv. Subacute sclerosing panencephalitis |
  v. Unspecified |
| Food poisoning, all causes | Trichinosis |
| Gastroenteritis, institutional outbreaks | Tuberculosis, active and latent |
| Giardiasis, except asymptomatic cases | Tularemia |
| Gonorrhea | Typhoid Fever |
| *Haemophilus influenzae b* disease, invasive | Verotoxin-producing *E. coli* infection indicator conditions, including |
| Hantavirus pulmonary syndrome | Hemolytic Uremic Syndrome (HUS) |
| Hemorrhagic fevers, including:
  i. Ebola virus disease |
  ii. Marburg virus disease |
  iii. Other viral causes |
  iv. Hantavirus pulmonary syndrome |
| Hepatitis, viral:
  i. Hepatitis A |
  ii. Hepatitis B |
  iii. Hepatitis C |
  iv. Hepatitis D (Delta hepatitis) |
| Herpes, neonatal | West Nile Virus illness, including:
  i. West Nile fever |
  ii. West Nile neurological manifestations |
| Human Immunodeficiency Virus (HIV) | Yellow Fever |
| Influenza | Yersiniosis |
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Acronyms

5-HT  serotonin
ACh  acetylcholine
ACT  assertive community treatment
ADHD  attention deficit hyperactivity disorder
AN  anorexia nervosa
ASD  autism spectrum disorder
ASPD  antisocial personality disorder
BN  bulimia nervosa
CT  community reinforcement approach
CTO  community treatment order
DA  dopamine
DZ  dizygotic
eCT  electroconvulsive therapy
EPS  extrapyramidal symptoms
ERBP  exposure with response prevention
EtiH  ethanol/alcohol
GAD  generalized anxiety disorder
GMC  general medical condition
IPT  interpersonal therapy
MDD  major depressive disorder
MDE  major depressive episode
MET  motivational enhancement therapy
MSE  mental status examination
NMS  neuroleptic malignant syndrome
NOS  not otherwise specified
NA  Narcotics Anonymous
NB  Neuroleptics
NOS  not otherwise specified
PD  personality disorder
PDD  pervasive developmental disorder
PTSD  post-traumatic stress disorder
rTMS  repetitive transcranial magnetic stimulation
SNRI  serotonin and norepinephrine reuptake inhibitors
SSRI  selective serotonin reuptake inhibitor
TCA  tricylic antidepressant

Suicide

Epidemiology

- attempted:completed = 20:1
- M:F = 1:4 for attempts, 3:1 for completed

Risk Factors

- epidemiologic factors
  - age: increases after age 14, second most common cause of death for ages 15-24, highest rates in persons >65 yr
  - sex: male
  - marital status: widowed/divorced
  - living situation: alone; no children <18 yr old in the household
  - other: stressful life events, access to firearms

- psychiatric disorders
  - mood disorders (15% lifetime risk in depression; higher in bipolar)
  - anxiety disorders (especially panic disorder)
  - schizophrenia (10-15% risk)
  - substance abuse (especially alcohol – 15% lifetime risk)
  - eating disorders (5% lifetime risk)
  - adjustment disorder
  - conduct disorder
  - personality disorders (borderline, antisocial)

- past history
  - prior suicide attempt
  - family history of suicide attempt/completion

Clinical Presentation

- symptoms associated with suicide
  - hopelessness
  - anhedonia
  - insomnia
  - severe anxiety
  - impaired concentration
  - psychomotor agitation
  - panic attacks

Approach

Every Patient: “Have you had any thoughts of wanting to hurt or kill yourself?”

- passive ideation: would rather not be alive but has no active plan for suicide
  - e.g. “I'd rather not wake up” or “I would not mind if a car hit me”
- active ideation
  - e.g. “I think about killing myself”
- plan: “Do you have a plan as to how you would end your life?”
- intent: “You talk about wanting to die, but are you planning to do this?” or “What has stopped you from ending your life?”
- past attempts: highest risk if previous attempt in past year
  - ask about lethality, outcome, medical intervention

Assessment of Suicidal Ideation

- onset and frequency of thoughts: “When did this start?” or “How often do you have these thoughts?”
- control over suicidal ideation: “Can you stop the thoughts or call someone for help?”
- lethality: “Do you want to end your life?” or “What do you think would happen if you actually took those pills?”
- access to means: “How will you get a gun?” or “Which bridge do you think you would go to?”

Suicidal Ideation Assessment

- Asking patients about suicide will not give them the idea or the incentive to commit suicide
- The best predictor of completed suicide is a history of attempted suicide
- The most common psychiatric disorders associated with completed suicide are mood disorders and alcohol abuse
Assessment of Suicide Attempt
- setting (isolated vs. others present/chance of discovery)
- planned vs. impulsive attempt, triggers/stressors
- substance use/intoxication
- medical attention (brought in by another person vs. brought in by self to ED)
- time lag from suicide attempt to ED arrival
- expectation of lethality, dying
- reaction to survival (guilt/remorse vs. disappointment/self-blame)

Management
- proper documentation of the clinical encounter and rationale for management is essential
- higher risk (hospitalization needs to be strongly considered)
  - patients with a plan, access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder
  - do not leave patient alone; remove potentially dangerous objects from room
  - if patient refuses to be hospitalized, consider involuntary admission as per state specific statutes
- lower risk
  - patients who are not actively suicidal, with no plan or access to lethal means
  - discuss protective factors and supports in their life, remind them of what they live for, promote survival skills that helped them through previous suicide attempts
  - make a safety plan and an agreement that they will
    - not harm themselves
    - avoid alcohol, drugs, and situations that may trigger suicidal thoughts
    - follow-up with you at a designated time
    - contact a health care worker, call a crisis line, or go to an emergency department if they feel unsafe or if their suicidal feelings return or intensify
- depression: consider hospitalization if symptoms severe or if psychotic features are present; otherwise outpatient treatment with good supports and SSRIs/SNRIs
- alcohol-related: usually resolves with abstinence for a few days; if not, suspect depression
- personality disorders: crisis intervention/confrontation, may or may not hospitalize
- schizophrenia/psychosis: hospitalization might be necessary
- parasuicide/self-mutilation: long-term psychotherapy with brief crisis intervention when necessary

Psychotic Disorders

Definition
- characterized by a significant impairment in reality testing
  - delusions or hallucinations (with/without insight into their pathological nature)
  - behaving in a disorganized way so that it is reasonable to infer that reality testing is disturbed

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Psychotic Symptoms</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Psychotic Disorder</td>
<td>≥1 positive symptoms of criterion A</td>
<td>&lt;1 mo</td>
</tr>
<tr>
<td>Schizophreniform Disorder</td>
<td>Criterion A</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Criterion A</td>
<td>&gt;6 mo</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>≥2 wk (with no mood symptoms)</td>
<td>&gt;1 mo</td>
</tr>
<tr>
<td>Delusional Disorder</td>
<td>Non-bizarre delusions, hallucinations</td>
<td>&gt;1 mo</td>
</tr>
<tr>
<td>2º to Substance Intoxication/ Withdrawal</td>
<td>Criterion A</td>
<td>During intoxication or ≤1 mo after withdrawal</td>
</tr>
<tr>
<td>2º to Mood Disorder</td>
<td>Delusions/hallucinations (mood congruent)</td>
<td>Psychosis may be present for the duration of the mood episode</td>
</tr>
</tbody>
</table>

Figure 1. Differentiating psychotic disorders with duration

Duration of Time Differentiates the following 3 Psychotic Disorders
- Brief Psychotic Disorder: < 1 month
- Schizophreniform Disorder: 1-6 months
- Schizophrenia: > 6 months

Delusions: fixed, false beliefs
Hallucinations: perceptual experiences without an external stimulus


**Differential Diagnosis of Psychosis**

- primary psychotic disorders: schizophrenia, schizophreniform, brief psychotic, schizoaffective, delusional disorder
- mood disorders: depression with psychotic features, bipolar disorder (manic or depressive episode with psychotic features)
- personality disorders: schizotypal, schizoid, borderline, paranoid, obsessive-compulsive
- general medical conditions: tumor, head trauma, dementia, delirium, metabolic, infection, stroke, temporal lobe epilepsy
- substance-induced psychosis: intoxication or withdrawal, prescribed medications, toxins

**Schizophrenia**

**DSM-5 Diagnostic Criteria for Schizophrenia**

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A. two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least one of these must be (1), (2), or (3)
   1. delusions
   2. hallucinations
   3. disorganized speech (e.g. frequent derailment or incoherence)
   4. grossly disorganized or catatonic behavior
   5. negative symptoms (i.e. diminished emotional expression or avolition)

B. for a significant portion of time since the onset of the disturbance, level of functioning in one or more major areas (e.g. work, interpersonal relations, self-care) is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning)

C. continuous signs of the disturbance persist for at least 6 mo. This 6 mo period must include at least 1 mo of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences)

D. schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods

E. the disturbance is not attributable to the physiological effects of a substance (e.g. drug of abuse, a medication) or another medical condition

F. if there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia are also present for at least 1 mo (or less if successfully treated)

**specifiers:** type of episode (e.g. first episode, multiple episodes, continuous), with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis

**Epidemiology**

- prevalence: 0.3–0.7%, M:F = 1:1
- mean age of onset: females late-20s; males early- to mid-20s
- suicide risk: 5-6% die by suicide, 20% attempt suicide

**Etiology**

- multifactorial: disorder is a result of interaction between both biological and environmental factors
  - genetic: 40% concordance in monozygotic (MZ) twins; 46% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected
  - neuroanatomy: decreased frontal lobe function; asymmetric temporal/limbic function; decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytotoxicar abnormalities
  - neuroendocrinology: abnormal growth hormone, prolactin, cortisol, and ACTH
  - neurochemistry: dopamine hypothesis: excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis while decreased dopamine in the prefrontal cortex may mediate negative and cognitive symptoms. GABA, glutamate, and ACh dysfunction are also thought to be involved

**Management of Acute Psychosis and Mania**

- Ensure safety of self, patient, and other patients
- Have an exit strategy
- Decrease stimulation
- Assume a non-threatening stance
- Do not use antidepressants or stimulants

**Differential Diagnosis of Psychosis**

- substance-induced psychosis: intoxication or withdrawal, prescribed medications, toxins

**Relationship Between Duration of Untreated Psychosis (DUP) and Outcome in First-Episode Schizophrenia**

Am J Psychiatry 2005;162:1795-1804

**Purpose:** To review the association between DUP and symptom severity at first treatment contact, and between DUP and treatment outcomes.

**Study Characteristics:** Critical review and meta-analysis of 43 studies with 4,177 patients.

**Participants:** Patients with non-affective psychotic disorders at or close to first treatment.

**Results:** Shorter DUP was associated with greater response to antipsychotic treatment, as measured by global psychopathology, positive symptoms, negative symptoms, and functional outcomes. At the time of treatment initiation, longer DUP was associated with the severity of negative symptoms but not with the severity of positive symptoms, global psychopathology, or neurocognitive function.

**Conclusions:** DUP may be a potentially modifiable prognostic factor.

---

**Suggested Further Reading**

- “Schizophrenia: A Common Condition with Multiple Facets.”
- “Understanding the Genetics of Schizophrenia.”
- neuropsychology: global defects seen in attention, language, and memory suggest lack of connectivity of neural networks
- environmental: indirect evidence of cannabis use, geographical variance, winter season of birth, obstetrical complications, and prenatal viral exposure

**Pathophysiology**

- neurodegenerative theory
  - natural history may be a rapid or gradual decline in function and ability to communicate
  - glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
- neurodevelopmental theory: abnormal development of the brain from prenatal life
  - neurons fail to migrate correctly, make inappropriate connections, and break down in later life
  - inappropriate apoptosis during neurodevelopment resulting in faulty connections between neurons

**Comorbidity**

- substance-related disorders
- anxiety disorders
- decreased life expectancy because of associated medical conditions (e.g. weight gain, diabetes, metabolic syndrome, CV/pulmonary disease)

**Management of Schizophrenia**

- biological
  - acute treatment and maintenance with antipsychotics ± anticonvulsants ± anxiolytics
- psychosocial
  - psychotherapy (individual, family, group): supportive, CBT
  - ACT: mobile mental health teams that provide individualized treatment in the community and help patients with medication adherence, basic living skills, social support, job placements, and community resources
  - social skills training, employment programs, disability benefits
  - housing (group home, boarding home, transitional home)

**Course and Prognosis**

- the majority of individuals display some type of prodromal phase
- course is variable: some individuals have exacerbations and remissions and others remain chronically ill; accurate prediction of the long-term outcome is not possible
- negative symptoms may be prominent early in the illness and may become more prominent and more disabling later on; positive symptoms appear and typically diminish with treatment
- over time: 1/3 improve, 1/3 remain the same, 1/3 worsen

**Schizophreniform Disorder**

- **diagnosis**: criteria A, D, and E of schizophrenia are met; an episode of the disorder lasts for at least 1 mo but <6 mo
- **specifiers**: with/if the symptoms have extended past 6 mo the diagnosis becomes schizophrenia
- **treatment**: similar to acute schizophrenia
- **prognosis**: better than schizophrenia; begins and ends more abruptly; good pre- and post-morbid function

**Brief Psychotic Disorder**

- **diagnosis**: criteria A1-A4, D, and E of schizophrenia are met; an episode of the disorder lasts for at least 1 d, but <1 mo with eventual full return to premorbid level of functioning
- **specifiers**: with/without marked stressors, with postpartum onset, with catatonia, current severity
- can occur after a stressful event or postpartum
- **treatment**: secure environment, antipsychotics, anxiolytics
- **prognosis**: good, self-limiting, should return to pre-morbid function within 1 mo

**Good Prognostic Factors**

- Acute onset
- Shorter duration of prodrome
- Female gender
- Good cognitive functioning
- Good premorbid functioning
- No family history
- Presence of affective symptoms
- Absence of structural brain abnormalities
- Good response to drugs
- Good support system
**Schizoaffective Disorder**

**DSM-5 Diagnostic Criteria for Schizoaffective Disorder**
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. an uninterrupted period of illness during which there is a major mood episode concurrent with Criterion A of schizophrenia

B. delusions or hallucinations for 2 or more wk in the absence of a major mood episode during the lifetime duration of the illness

C. symptoms that meet criteria for a major mood episode are present for the majority of the total duration of the active and residual periods of the illness

D. the disturbance is not attributable to the effects of a substance or another medical condition

- **specifiers**: bipolar type, depressive type, with catatonia, type of episode, severity
- one-third as prevalent as schizophrenia; schizoaffective disorder bipolar type more common in young adults, schizoaffective disorder depressive type more common in older adults
- depressive symptoms correlated with higher suicide risk
- **treatment**: antipsychotics, mood stabilizers, antidepressants
- **prognosis**: between that of schizophrenia and of mood disorder

**Delusional Disorder**

**DSM-5 Diagnostic Criteria for Delusional Disorder**
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A. the presence of one (or more) delusions with a duration of ≥1 mo

B. criterion A for schizophrenia has never been met

- **Note**: hallucinations, if present, are not prominent and are related to the delusional theme

C. apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behavior is not obviously bizarre or odd

D. if manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods

E. the disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder

- **subtypes**: erotomanic, grandiose, jealous, persecutory, somatic, mixed, unspecified
  - further specify: bizarre content, type of episode (e.g. first episode, multiple episode), severity
- **treatment**: psychotherapy, antipsychotics, antidepressants
- **prognosis**: chronic, unremitting course but high level of functioning; a portion will progress to schizophrenia

**Mood Disorders**

**Definitions**
- mood disorders are defined by the presence of mood episodes
- mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration (e.g. major depressive, manic, mixed, hypomanic)
- types of mood disorders include
  - depressive (major depressive disorder, persistent depressive disorder)
  - bipolar (bipolar I/II disorder, cyclothymia)
  - secondary to GMC, substances, medications

**Medical Workup of Mood Disorder**
- **routine screening**: physical exam, CBC, thyroid function test, electrolytes, extended electrolytes, urinalysis, drug screen
- **additional screening**: neurological consultation, chest x-ray, ECG, CT

**Mood Episodes**

**DSM-5 Criteria for Major Depressive Episode**
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A. ≥5 of the following symptoms have been present during the same 2-wk period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia)

- **Note**: Do not include symptoms that are clearly attributable to another medical condition
  - depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others

**Criteria for Depression (≥5)**

MSIGECAPS
- Mood: depressed
- Sleep: increased/decreased
- Interest: decreased
- Guilt
- Energy: decreased
- Concentration: decreased
- Appetite: increased/decreased
- Psychomotor: agitation/retardation
- Suicidal ideation
PS7 Psychiatry Mood Disorders Essential Med Notes 2015

- markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
- significant and unintentional weight loss/weight gain, or decrease/increase in appetite nearly every day
- insomnia or hypersomnia nearly every day
- psychomotor agitation or retardation nearly every day
- fatigue or loss of energy nearly every day
- feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. the episode is not attributable to the direct physiological effects of a substance or a GMC

DSM-5 Criteria for Manic Episode
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting ≥1 wk and present most of the day, nearly every day (or any duration if hospitalization is necessary)
B. during the period of mood disturbance and increased energy or activity, ≥3 of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behavior:
- inflated self-esteem or grandiosity
- decreased need for sleep (e.g. feels rested after only 3 h of sleep)
- more talkative than usual or pressure to keep talking
- flight of ideas or subjective experience that thoughts are racing
- distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
- increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
- excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained shopping sprees, sexual indiscretions, or foolish business investments)
C. the mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
D. the episode is not attributable to the physiological effects of a substance or another medical condition
Note: A full manic episode that emerges during antidepressant treatment but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode, and therefore, a bipolar I diagnosis
Note: Criteria A-D constitute a manic episode. At least one lifetime manic episode is required for the diagnosis of bipolar I disorder

Hypomanic Episode
- criterion A and B of a manic episode is met, but duration is ≥4 d
- episode associated with an uncharacteristic change in functioning that is observable by others
- change in function is not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features

Depressive Disorders

MAJOR DEPRESSIVE DISORDER

DSM-5 Diagnostic Criteria for Major Depressive Disorder (MDD), Single Episode (vs. Recurrent)
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. presence of a single MDE (vs. recurrent, which requires presence of two or more MDEs; to be considered separate episodes, there must be an interval of at least 2 consecutive mo in which criteria are not met for a MDE)
B. the MDE is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder NOS
C. there has never been a manic episode or a hypomanic episode
• **Note:** this exclusion does not apply if all of the manic-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of another medical condition

• **specifiers:** with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, seasonal pattern

**Epidemiology**

• prevalence: 12.2%
  - lifetime prevalence: male 2.9%, female 5%
  - annual prevalence: peak prevalence age 15-25 yr (M:F = 1:2)

**Etiology**

• biological
  - genetic: 65-75% MZ twins; 14-19% DZ twins
  - neurotransmitter dysfunction: decreased activity of 5HT, NE, and DA at the level of the synapse; changes in GABA and glutamate; changes in brain circuitry
  - neuroendocrine dysfunction: increased production of corticotropins causing excessive HPA axis activity
  - neuroanatomy: smaller frontal lobes and hippocampal volume; increased ventricle sizes
  - neurophysiologic: decreased REM latency and slow-wave sleep; increased REM length
  - secondary to another medical condition

  • psychosocial
    - psychodynamic (e.g. low self-esteem)
    - cognitive (e.g. negative thinking)
    - environmental factors (e.g. job loss, bereavement, history of abuse, early life adversity)
    - comorbid psychiatric diagnoses (e.g. anxiety, substance abuse, developmental disability, dementia, eating disorder)

**Risk Factors**

• sex: F>M
• age: onset between 25-50 yr of age
• family history: depression, alcohol abuse, sociopathy
• childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
• personality: insecure, dependent, obsessional
• recent stressors: illness, financial, legal
• postpartum <6 mo
• lack of intimate, confiding relationships or social isolation

**Treatment**

• biological: antidepressants primarily; could also consider lithium, antipsychotics, anxiolytics, light therapy, ECT, rTMS
• psychological
  - individual therapy (psychodynamic, interpersonal, CBT), family therapy, group therapy
  - social: vocational rehabilitation, social skills training
  - experimental: MST, deep brain stimulation, vagal nerve stimulation
  - studies suggest CBT with pharmacotherapy results in better outcomes

**Prognosis**

• one year after diagnosis of a MDE without treatment: 40% of individuals still have symptoms that are sufficiently severe to meet criteria for a full MDE, 20% continue to have some symptoms that no longer meet criteria for a MDE, 40% have no mood disorder

**PERSISTENT DEPRESSIVE DISORDER**

**DSM-5 Diagnostic Criteria for Persistent Depressive Disorder**

*Note: in DSM-IV-TR this was referred to as Dysthymia*

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A. depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for ≥2 yr

  • Note: In children and adolescents, mood can be irritable and duration must be at least 1 yr

B. presence, while depressed, of ≥2 of the following

  • poor appetite or overeating
  • insomnia or hypersomnia
  • low energy or fatigue
  • low self-esteem
  • poor concentration or difficulty making decisions
  • feelings of hopelessness

Antidepressants for Depression in Medical Illness
Cochrane DB Syst Rev 2010; Issue 3

This systematic review and meta-analysis of 51 RCTs (3,603 patients) compared antidepressants to placebo in patients with a physical disorder (e.g. cancer, MI) who have been diagnosed as depressed (including major depression, adjustment disorder, and dysthymia).

**Conclusions:** Antidepressants, including SSRIs and TCAs, cause a significant improvement in patients with a physical illness, as compared to placebo.
C. during the 2 yr period (1 yr for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 mo at a time
D. criteria for a major depressive disorder may be continuously present for 2 yr
E. the disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder
F. the symptoms are not due to the direct physiological effects of a substance or another medical condition
G. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Epidemiology
- point prevalence: 3%; life prevalence: 6%; M:F = 1:2-3

Treatment
- psychological
  - principal treatment for persistent depressive disorder
  - individual, group, and family therapy
- biological
  - antidepressant therapy (SSRIs/SNRIs) as an outpatient

Bipolar Disorders

BIPOLAR I / BIPOLAR II DISORDER

Definition
- Bipolar I Disorder
  - disorder in which at least one manic episode has occurred
  - commonly accompanied by at least 1 MDE but not required for diagnosis
- Bipolar II Disorder
  - disorder in which there is at least 1 MDE and at least 1 hypomanic episode
  - no past manic or mixed episodes

Epidemiology
- prevalence: 0.6-0.9%; M:F = 1:1
- age of onset: teens to 20s

Risk Factors
- high SES
- genetic: 60-65% of bipolar patients have family history of major mood disorders

Classification
- classification of bipolar disorder involves describing the current or most recent mood episode as either manic, hypomanic, or depressed. The same specifiers for MDD can be used

Treatment
- biological: lithium, anticonvulsants, antipsychotics, ECT; monotherapy with antidepressants should be avoided
- psychological: supportive or psychodynamic psychotherapy, CBT, IPT or interpersonal social rhythm therapy, family focused treatment
- social: vocational rehabilitation, consider leave of absence from school/work, assess capacity to manage finances, drug and EtOH cessation, sleep hygiene, social skills training, education for family members

Course and Prognosis
- high suicide rate (15% mortality from suicide)
- relapsing and remitting course with alternating manic and depressive episodes; depressive symptoms tend to occur more frequently and last longer than manic episodes
- patients spend almost half of their lives symptomatic
- may switch rapidly between depression and mania without any period of euthymia in between
- high recurrence rate for mania ~ 90% will have a subsequent episode in the next 5 yr

Patients with bipolar disorder are at higher risk for suicide when they switch from mania to depression, especially as they become aware of consequences of their behavior during the manic episode

Treatment of bipolar depression must be done extremely cautiously, as a switch from depression to mania can result; monotherapy with antidepressants should be avoided
CYCLOTHYMIA

Diagnosis
- presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for full hypomanic episode or MDE) for ≥2 yr; never without symptoms for >2 mo
- never have met criteria for MDE, manic or hypomanic episodes
- symptoms are not due to the direct physiological effects of a substance or GMC
- symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Treatment
- similar to Bipolar I: mood stabilizer ± psychotherapy

Anxiety Disorders

Definition
- anxiety is a universal human characteristic involving tension, apprehension, or even terror
- serves as an adaptive mechanism to warn about an external threat by activating the sympathetic nervous system (fight or flight)
- manifestations of anxiety can be described through
  - physiology: main brain structure involved is the amygdala (fear conditioning); neurotransmitters involved include 5-HT, cholecystokinin, epinephrine, norepinephrine, DA
  - psychology: one’s perception of a given situation is distorted which causes one to believe it is threatening in some way
  - behavior: once feeling threatened, one responds by escaping or facing the situation, thereby causing a disruption in daily functioning
- anxiety becomes pathological when
  - fear is greatly out of proportion to risk/severity of threat
  - response continues beyond existence of threat or becomes generalized to other similar or dissimilar situations
  - social or occupational functioning is impaired

Differential Diagnosis

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<td><strong>Other Psychiatric Disorders</strong></td>
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Medical Workup of Anxiety Disorder
- routine screening: physical exam, CBC, thyroid function test, electrolytes, urinalysis, urine drug screening
- additional screening: neurological consultation, chest x-ray, ECG, CT

Panic Disorder

DSM-5 Diagnostic Criteria for Panic Disorder
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A. recurrent unexpected panic attacks; a panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur
  - palpitations, pounding heart, or accelerated heart rate
  - sweating
  - trembling or shaking
  - sensations of shortness of breath or smothering
  - feelings of choking
  - chest pain or discomfort
  - nausea or abdominal distress
feeling dizzy, unsteady, light-headed, or faint
chills or heat sensations
paresthesias (numbness or tingling sensations)
dererealization (feelings of unreality) or depersonalization (being detached from oneself)
fear of losing control or “going crazy”
fear of dying

B. at least one of the attacks has been followed by ≥1 mo of one or both of the following
persistent concern or worry about additional panic attacks or their consequences
a significant maladaptive change in behavior related to the attacks

C. the disturbance is not attributable to the physiological effects of a substance or another medical condition

D. the disturbance is not better explained by another mental disorder

Epidemiology
• prevalence: 2-5% (one of the top five most common reasons to see a family doctor); M:F = 1:2-3
• onset: average early-mid 20s, familial pattern

Treatment
• psychological
  • CBT: interoceptive exposure (eliciting symptoms of a panic attack and learning to tolerate the symptoms without coping strategies), cognitive restructuring (addressing underlying beliefs regarding the panic attacks), relaxation techniques (visualization, box-breathing)
  • pharmacological
    • SSRIs: fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline
    • SNRI: venlafaxine
    • with SSRI/SNRIs start with low doses, titrate up slowly
    • anxiety disorders often require treatment at higher doses for a longer period of time than depression (i.e. full response may take up to 12 wk)
    • to prevent non-compliance due to physical side effects, explain symptoms to expect prior to initiation of therapy
    • other antidepressants (TCAs, mirtazapine, MAOIs)
      • consider avoiding bupropion due to stimulating effects
    • benzodiazepines (short-term, low dose, regular schedule, long half-life, avoid prn use)

Prognosis
• 6-10 yr post-treatment: 30% well, 40-50% improved, 20-30% no change or worse
• clinical course: chronic, but episodic with psychosocial stressors

Agoraphobia

DSM-5 Diagnostic Criteria for Agoraphobia
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. marked fear or anxiety about two (or more) of the following five situations
  • using public transportation
  • being in open spaces
  • being in enclosed places
  • standing in line or being in a crowd
  • being outside of the home alone

B. the individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms

C. the agoraphobic situations almost always provoke fear or anxiety

D. the agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety

E. the fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context

F. the fear, anxiety, or avoidance is persistent, typically lasting for ≥6 mo

G. the fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

H. if another medical condition is present, the fear, anxiety, or avoidance is clearly excessive

I. the fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder and are not related exclusively to obsessions, perceived defects or flaws in physical appearance, reminders of traumatic events, or fear of separation

Note: agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual’s presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned

• treatment: as per panic disorder
Generalized Anxiety Disorder

DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder

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A. excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance)
B. the individual finds it difficult to control the worry
C. the anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 mo)
   1. restlessness or feeling keyed up or on edge
   2. being easily fatigued
   3. difficulty concentrating or mind going blank
   4. irritability
   5. muscle tension
   6. sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D. the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition
F. the disturbance is not better explained by another mental disorder

Epidemiology

- 1 yr prevalence: 3-8%; M:F = 1:2
  - if considering only those receiving inpatient treatment, ratio is 1:1
- most commonly presents in early adulthood

Treatment

- lifestyle: caffeine and EtOH avoidance, sleep hygiene
- psychological: CBT including relaxation techniques, mindfulness
- biological
  - SSRIs and SNRIs are 1st line (paroxetine, escitalopram, sertraline, venlafaxine XL)
  - 2nd line: bupropion (caution due to stimulating effects), buspirone (tid dosing)
  - add-on benzodiazepines (short-term, low dose, regular schedule, long half-life, avoid prn)
  - β-blockers not recommended

Prognosis

- chronically anxious adults become less so with age
- depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress
- difficult to treat

Phobic Disorders

Specific Phobia

- definition: marked and persistent fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
- lifetime prevalence 12-16%; M:F ratio variable
- types: animal/insect, environment (heights, storms), blood/injection/injury, situational (airplane, closed spaces), other (loud noise, clowns)

Social Phobia (Social Anxiety Disorder)

- definition: marked and persistent fear of social or performance situations in which one is exposed to unfamiliar people or to possible scrutiny by others; fearing he/she will act in a way that may be humiliating or embarrassing (e.g. public speaking, initiating or maintaining conversation, dating, eating in public)
- 12 mo prevalence rate may be as high as 7%; F>M

Diagnostic Criteria for Phobic Disorders

- exposure to stimulus almost invariably provokes an immediate anxiety response; may present as a panic attack
- person recognizes fear as excessive or unreasonable
- situations are avoided or endured with anxiety/distress
- significant interference with daily routine, occupational/social functioning, and/or marked distress
Treatment
- psychological
  - cognitive behavior therapy (focusing on both in vivo and virtual exposure therapy, gradually facing feared situations)
  - behavioral therapy is more efficacious than medication
- biological
  - SSRIs/SNRIs
  - β-blockers or benzodiazepines in acute situations (e.g. public speaking)

Prognosis
- chronic

Obsessive-Compulsive Disorder

DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder
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A. presence of obsessions, compulsions, or both
  - obsessions are defined by (1) and (2)
    1. recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and that in most individuals cause marked anxiety or distress
    2. the individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e. by performing a compulsion)
  - compulsions are defined by (1) and (2)
    1. repetitive behaviors (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly
    2. the behaviors or mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviors or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive
B. the obsessions or compulsions are time-consuming (e.g. take >1 h/d) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. the obsessive-compulsive symptoms are not attributable to the physiological effects
D. the disturbance is not better explained by the symptoms of another mental disorder

Epidemiology
- 12 mo prevalence 1.1-1.8%; females affected at slightly higher rates than males
- rate of OCD in first-degree relatives is higher than in the general population

Treatment
- CBT: exposure with response prevention (ERP) – involves exposure to feared situations with the addition of preventing the compulsive behaviors; cognitive strategies include challenging underlying beliefs
- pharmacotherapy: SSRIs/SNRIs, clomipramine; adjunctive risperidone

Prognosis
- tends to be refractory and chronic

Trauma- and Stressor-Related Disorders

Post-Traumatic Stress Disorder

DSM-5 Diagnostic Criteria for Post-Traumatic Stress Disorder
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A. exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways
  1. directly experiencing the traumatic event(s)
  2. witnessing, in person, the event(s) as it occurred to others
  3. learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental
  4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g. first responders collecting human remains: police officers repeatedly exposed to details of child abuse)

Acute Stress Disorder
- May be a precursor to PTSD
- Similar symptoms to PTSD
- Symptoms persist 3 d after a trauma until 1 mo after the exposure
B. presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred
   1. recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)
   2. recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s)
   3. dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring
   4. intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
   5. marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
C. persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following
   1. avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)
   2. avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)
D. negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following
   1. inability to remember an important aspect of the traumatic event(s)
   2. persistent and exaggerated negative beliefs or expectations about oneself, others, or the world
   3. persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others
   4. persistent negative emotional state (e.g. fear, horror, anger, guilt, or shame)
   5. markedly diminished interest or participation in significant activities
   6. feelings of detachment or estrangement from others
   7. persistent inability to experience positive emotions
E. marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following
   1. irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects
   2. reckless or self-destructive behavior
   3. hypervigilance
   4. exaggerated startle response
   5. problems with concentration
   6. sleep disturbance (e.g. difficulty falling or staying asleep or restless sleep)
F. duration of the disturbance (criteria B, C, D, and E) is >1 mo
G. the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
H. the disturbance is not attributable to the physiological effects of a substance or another medical condition

Epidemiology
- lifetime prevalence (DSM-IV criteria): 8.7%
- men's trauma is most commonly combat experience/physical assault; women's trauma is usually physical or sexual assault

Treatment
- CBT: exposure therapy, challenge dysfunctional beliefs, emotional regulation techniques (e.g. breathing, relaxation)
- biological
  - SSRIs
  - benzodiazepines (for acute anxiety)
  - adjunctive atypical antipsychotics (risperidone, olanzapine)
- Eye Movement Desensitization and Reprocessing (EMDR): an experimental method of reprocessing memories of distressing events by recounting them while using a form of dual attention stimulation such as eye movements, bilateral sound, or bilateral tactile stimulation (its use is controversial because of limited evidence)

Complications
- substance abuse, relationship difficulties, depression, impaired social and occupational functioning disorders, personality disorders
**Adjustment Disorder**

**DSM-5 Diagnostic Criteria for Adjustment Disorder**

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A. the development of emotional or behavioral symptoms in response to an identifiable stressor(s) occurring within 3 mo of the onset of the stressor(s)

B. these symptoms or behaviors are clinically significant as evidenced by either of the following:
   - marked distress that is in excess of what would be expected from exposure to the stressor
   - significant impairment in social or occupational (academic) functioning

C. the stress-related disturbance does not meet criteria for another mental disorder and is not merely an exacerbation of a pre-existing mental disorder

D. the symptoms do not represent normal bereavement

E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 mo

- **specifiers**: with depressed mood, with anxiety, with mixed anxiety/depression, with conduct disturbance, with mixed disturbance of conduct/emotions, unspecified

**Classification**

- types of stressors
  - single (e.g. termination of romantic relationship)
  - multiple (e.g. marked business difficulties and marital problems)
  - recurrent (e.g. seasonal business crises)
  - continuous (e.g. living in a crime-ridden neighborhood)
  - developmental events (e.g. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)

**Epidemiology**

- **M=F**

**Treatment**

- brief psychotherapy (group, individual), crisis intervention
- **biological**
  - benzodiazepines may be used for those with anxiety symptoms (short-term, low-dose, regular schedule)
  - SSRIs for both depression and anxiety symptoms

**Bereavement**

**Clinical Presentation**

- length and characteristics of “normal” bereavement are variable between individuals/cultures
- may present with symptoms of MDE/MDD but individual regards depressed mood as normal
- presence of following symptoms may indicate abnormal grief/presence of MDD
  - guilt about things other than actions taken or not taken by the survivor at the time of death
  - thoughts of death other than the survivor feeling that they would be better off dead or should have died with the deceased person; morbid preoccupation with worthlessness
  - marked psychomotor retardation; prolonged and marked functional impairment
  - hallucinatory experiences other than thinking that the survivor hears the voice of or transiently sees the image of the deceased person
- after 12 mo, if patient continues to yearn/long for the deceased, experience intense sorrow/emotional pain in response to the death, remain preoccupied with the deceased or with their circumstance of death, then may start to consider a diagnosis of “persistent complex bereavement disorder”

**Risk Factors for Poor Bereavement Outcome**

- Poor social supports
- Unanticipated death or lack of preparation for death
- Highly dependent relationship with deceased
- High initial distress
- Other concurrent stresses and losses
- Death of a child
- Pre-existing psychiatric disorders, especially depression and separation anxiety
Neurocognitive Disorders

Delirium

- see Neurology, N19 and Geriatric Medicine, GM3

DSM-5 Diagnostic Criteria for Delirium
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A. a disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment)
B. the disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day
C. an additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception)
D. the disturbances in criteria A and C are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma
E. there is evidence from the history, physical exam, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies

Clinical Presentation and Assessment
- common symptoms
  - wandering attention
  - distractibility
  - disorientation (time, place, rarely person)
  - misinterpretations, illusions, hallucinations
  - speech/language disturbances (dysarthria, dysnomia, dysgraphia)
  - affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
  - shifts in psychomotor activity (grasping/picking at clothes, attempts to get out of bed when unsafe, sudden movements, sluggishness, lethargy)
- Folstein Mini Mental Status Exam is helpful to assess baseline of altered mental state (i.e. score will improve as symptoms resolve)

Risk Factors
- hospitalization (incidence 10-56%)
- nursing home residents (incidence 60%)
- polypharmacy (e.g. anticholinergic)
- childhood (e.g. febrile illness, anticholinergic use)
- old age (especially males)
- severe illness (e.g. cancer, AIDS)
- pre-existing cognitive impairment or brain pathology
- recent anesthesia
- substance abuse

Etiology (I WATCH DEATH)
- Infectious (encephalitis, meningitis, UTI, pneumonia)
- Withdrawal (alcohol, barbiturates, benzodiazepines)
- Acute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
- Trauma (head injury, post-operative)
- CNS pathology (stroke, hemorrhage, tumor, seizure disorder, Parkinson’s)
- Hypoxia (anemia, cardiac failure, pulmonary embolus)
- Deficiencies (vitamin B12, folic acid, thiamine)
- Endocrinopathies (thyroid, glucose, parathyroid, adrenal)
- Acute vascular (shock, vasculitis, hypertensive encephalopathy)
- Toxins: substance use, sedatives, opioids (especially morphine), anesthetics, anticholinergics, anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
- Heavy metals (arsenic, lead, mercury)

Investigations
- standard: CBC and differential, electrolytes, Ca++, PO4-3, Mg++, glucose, ESR, LFTs, Cr, BUN, TSH, vitamin B12, folate, albumin, urine C&S, R&M
- as indicated: ECG, CXR, CT head, toxicology/heavy metal screen, VDRL, HIV, LP, EEG
- indications for CT head: focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, history of cancer
Management

- intrinsic
  - identify and treat underlying cause immediately
  - stop all non-essential medications
  - maintain nutrition, hydration, electrolyte balance and monitor vitals
- extrinsic
  - environment should be quiet and well lit
  - optimize hearing and vision
  - room near nursing station for closer observation; constant care if patient jumping out of bed, pulling out lines
  - family member present for reassurance and re-orientation
  - calendar, clock for orientation cues
- biological
  - low dose antipsychotics
  - haloperidol has the most evidence; reasonable alternatives include risperidone, olanzapine, or quetiapine
  - benzodiazepines only to be used in alcohol withdrawal delirium; otherwise, can worsen delirium
  - physical restraints if patient becomes violent

Prognosis

- up to 50% 1 yr mortality rate after episode of delirium

Major Neurocognitive Disorder/Dementia

- see Neurology, N19

DSM-5 Diagnostic Criteria for Major Neurocognitive Disorder
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A. evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on
  1. concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function;
  2. a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment

B. the cognitive deficits interfere with independence in everyday activities (i.e. at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)

C. the cognitive deficits do not occur exclusively in the context of a delirium

D. the cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia)

- specify whether due to

  | Alzheimer’s disease | Traumatic brain injury | Huntington’s disease |
  | Frontotemporal lobar degeneration | Substance/medication use | Another medical condition |
  | Lewy body disease | HIV infection | Multiple etiologies |
  | Vascular disease | Prion disease | Unspecified |
  | Parkinson’s disease |

Epidemiology

- prevalence increases with age: 10% in patients >65 yr of age; 25% in patients >85 yr of age
- prevalence is increased in people with Down’s syndrome and head trauma
- Alzheimer’s disease comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia neurocognitive disorder – see Neurology, N19)
- average duration of illness from onset of symptoms to death is 8-10 yr

Subtypes

- with or without behavioral disturbance (e.g. wandering, agitation)
- early onset: age of onset <65 yr
- late onset: age of onset >65 yr

Investigations (Rule Out Reversible Causes)

- standard: see Delirium
- as indicated: VDRL, HIV, SPECT, CT head in dementia
indications for CT head: same as for delirium, plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 mo), dementia of relatively short duration (<2 yr), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/ seizures)

Management
- see Neurology, N22 for further management
- treat underlying medical problems and prevent others
- provide orientation cues for patient (e.g. clock, calendar)
- provide education and support for patient and family (e.g. day programs, respite care, support groups, home care)
- consider long-term care plan (nursing home) and power of attorney/living will
- inform Ministry of Transportation about patient's inability to drive safely
- consider pharmacological therapy
  - cholinesterase inhibitors (e.g. donepezil [Aricept®]) for mild to severe disease
  - NMDA receptor antagonist (e.g. memantine) for moderate to severe disease
  - low-dose neuroleptics (e.g. risperidone, quetiapine), antidepressants or trazodone if behavioral or emotional symptoms prominent – start low and go slow
  - reassess pharmacological therapy every 3 mo

Table 3. Comparison of Dementia, Delirium, and Pseudodementia of Depression

<table>
<thead>
<tr>
<th></th>
<th>Dementia/Major Neurocognitive Disorder</th>
<th>Delirium</th>
<th>Pseudodementia of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Gradual/step-wise decline</td>
<td>Acute (h-d)</td>
<td>Subacute</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Months-years</td>
<td>Days-weeks</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Natural History</strong></td>
<td>Progressive</td>
<td>Fluctuating, reversible</td>
<td>Recurrent</td>
</tr>
<tr>
<td></td>
<td>Usually irreversible</td>
<td>High morbidity/mortality in very old</td>
<td>Usually reversible</td>
</tr>
<tr>
<td><strong>Level of Consciousness</strong></td>
<td>Normal</td>
<td>Fluctuating (over 24 h)</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Attention</strong></td>
<td>Not initially affected</td>
<td>Decreased (wandering, easy distraction)</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Intact initially</td>
<td>Impaired (usually to time and place), fluctuates</td>
<td>Intact</td>
</tr>
<tr>
<td><strong>Behavior</strong></td>
<td>Disinhibition, impairment in ADL/IADL, personality change, loss of social graces</td>
<td>Severe agitation/retardation</td>
<td>Importuning, self-harm/suicide</td>
</tr>
<tr>
<td><strong>Psychomotor</strong></td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
<td>Slowing</td>
</tr>
<tr>
<td><strong>Sleep Wake Cycle</strong></td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep wake cycle</td>
<td>Early morning awakening</td>
</tr>
<tr>
<td><strong>Mood and Affect</strong></td>
<td>Labile but not usually anxious</td>
<td>Anxious, irritable, fluctuating</td>
<td>Depressed, stable</td>
</tr>
<tr>
<td><strong>Cognition</strong></td>
<td>Decreased executive functioning, paucity of thought</td>
<td>Fluctuating preceded by mood changes</td>
<td>Fluctuating</td>
</tr>
<tr>
<td><strong>Memory Loss</strong></td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
<td>Recent</td>
</tr>
<tr>
<td><strong>Language</strong></td>
<td>Agnosia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia)</td>
<td>Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes</td>
<td>Not affected</td>
</tr>
<tr>
<td><strong>Delusions</strong></td>
<td>Compensatory</td>
<td>Nightmarish and poorly formed</td>
<td>Nihilistic, somatic</td>
</tr>
<tr>
<td><strong>Hallucinations</strong></td>
<td>Variable</td>
<td>Visual common</td>
<td>Less common, auditory predominates</td>
</tr>
<tr>
<td><strong>Quality of Hallucinations</strong></td>
<td>Vacuous/bland</td>
<td>Frightening/bizarre</td>
<td>Self-deprecatory</td>
</tr>
<tr>
<td><strong>Medical Status</strong></td>
<td>Variable</td>
<td>Acute illness, drug toxicity</td>
<td>Rule out systemic illness, medications</td>
</tr>
</tbody>
</table>

Substance-Related and Addictive Disorders

Epidemiology
- 47% of those with substance abuse have mental health problems
- 29% of those with a mental health disorder have a substance use disorder
- 47% of those with schizophrenia and 25% of those with an anxiety disorder have a substance use disorder

Substance Use Disorders
- substance use disorders are measured on a continuum from mild to severe; 2-3 criteria is required for a mild substance use disorder diagnosis, 4-5 is moderate, and 6-7 is severe
- each specific substance can be addressed as a separate use disorder (e.g. alcohol use disorder, stimulant use disorder) and diagnosed utilizing the same overarching criteria
- criteria for substance use disorders
  - hazardous use
social/interpersonal problems related to use
- neglected major roles to use
- withdrawal
- tolerance
- use large amounts/longer
- repeated attempts to quit/control use
- use for longer duration/larger amount than intended
- physical/psychological problems related to use
- activities given up to use
- cravings

Classification of Substances

<table>
<thead>
<tr>
<th>Depressants</th>
<th>Alcohol, Opioids, Barbiturates, Benzodiazepines, GHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td>Amphetamines, Methylphenidate, Cocaine</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>Cannabis, LSD, PCP, Ketamine, Psilocybin</td>
</tr>
</tbody>
</table>

Nicotine
- see Family Medicine, FM10

Alcohol
- see Family Medicine, FM12 and Emergency Medicine, ER53

History
- CAGE: validated screening questionnaire
  - C ever felt the need to Cut down on drinking?
  - A ever felt Annoyed at criticism of your drinking?
  - G ever feel Guilty about your drinking?
  - E ever need a drink first thing in morning (Eye opener)?
  - for men, a score of ≥2 is a positive screen; for women, a score of ≥1 is a positive screen
  - if positive CAGE, then assess further to distinguish between problem drinking and alcohol dependence

General Assessment
- When was your last drink?
- Do you have to drink more to get the same effect?
- Do you get shaky or nauseous when you stop drinking?
- Have you ever had a withdrawal seizure?
- How much time and effort do you put into obtaining alcohol?
- Has your drinking affected your ability to work, go to school, or have relationships?
- Have you suffered any legal consequences?
- Has your drinking caused any medical problems?

Table 4. Canada’s Low-Risk Alcohol Drinking Guidelines

<table>
<thead>
<tr>
<th>Moderate Drinking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men: 3 or less/d (≤15/wk)</td>
</tr>
</tbody>
</table>

Alcohol Intoxication
- legal limit for impaired driving is 10.6 mmol/L (50 mg/dL) reached by 2-3 drinks/h for men and 1-2 drinks/h for women
- coma can occur with >60 mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)

Alcohol Withdrawal
- occurs within 12-48 h after prolonged heavy drinking and can be life-threatening
- alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced
  - stage 1 (onset 12-18 h after last drink): "the shakes" tremor, sweating, agitation, anorexia, cramps, diarrhea, sleep disturbance
  - stage 2 (onset 7-38 h): alcohol withdrawal seizures, usually tonic-clonic, nonfocal and brief
  - stage 3 (onset 48 h): visual, auditory, olfactory or tactile hallucinations
  - stage 4 (onset 3-5 d): delirium tremens, confusion, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (fever, tachycardia, HTN)
  - course: almost completely reversible in young; elderly often left with cognitive deficits
  - mortality rate 20% if untreated

Delirium Tremens
(Alcohol Withdrawal Delirium)
- Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)
- Hand tremor
- Insomnia
- Psychomotor agitation
- Anxiety
- Nausea or vomiting
- Tonic-clonic seizures
- Visual/tactile/auditory hallucinations
- Persecutory delusions

A “Standard Drink”
- Spirit (40%): 1.5 oz. or 43 mL
- Table Wine (12%): 5 oz. or 142 mL
- Fortified Wine (18%): 3 oz. or 85 mL
- Regular Beer (5%): 12 oz. or 341 mL

OR
- 1 pint of beer = 1.5 SD
- 1 bottle of wine = 5 SD
- 1 “mickey” = 8 SD
- “26-er” = 17 SD
- “40 oz.” = 27 SD

Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)
Management of Alcohol Withdrawal
- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
  - areas of assessment include
    - nausea and vomiting
    - tactile disturbances
    - tremor
    - auditory disturbances
    - agitation
    - paroxysmal sweats
    - visual disturbances
    - anxiety
    - headache, fullness in head
    - orientation and clouding of sensorium
  - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67
    - mild <10
    - moderate 10-20
    - severe >20

Table 5. CIWA-A Scale Treatment Protocol for Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Basic Protocol</th>
<th>Diazepam 20 mg PO q1-2h pm until CIWA-A &lt; 10 points</th>
<th>Observe 1-2 h after last dose and re-assess on CIWA-A scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive care (hydration and nutrition)</td>
<td>Thiamine 100 mg IM then 100 mg PO OD for 3 d</td>
<td></td>
</tr>
<tr>
<td>History of Withdrawal Seizures</td>
<td>Diazepam 20 mg PO q1h for minimum of three doses regardless of subsequent CIWA scores</td>
<td></td>
</tr>
<tr>
<td>If age &gt;65 or patient has severe liver disease, severe asthma or respiratory failure</td>
<td>Use a short acting benzodiazepine</td>
<td>Lorazepam PO/SL/IM 1-4 mg q1-2h</td>
</tr>
<tr>
<td>If Hallucinations are present</td>
<td>Haloperidol 2.5 mg IM/PO q1-4h – max 5 doses/d or atypical antipsychotics (olanzapine, risperidone)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold)</td>
<td></td>
</tr>
<tr>
<td>Admit to Hospital if</td>
<td>Still in withdrawal after &gt;80 mg of diazepam</td>
<td>Delirium tremens, recurrent arrhythmias, or multiple seizures</td>
</tr>
<tr>
<td></td>
<td>Medically ill or unsafe to discharge home</td>
<td></td>
</tr>
</tbody>
</table>

Wernicke-Korsakoff Syndrome
- alcohol-induced amnestic disorders due to thiamine deficiency
- necrotic lesions: mammillary bodies, thalamus, brainstem
- Wernicke's encephalopathy (acute and reversible): triad of nystagmus (CN VI palsy), ataxia, and confusion
- Korsakoff's syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and confabulations; cannot occur during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal
- management
  - Wernicke's: thiamine 100 mg PO OD x 1-2 wk
  - Korsakoff's: thiamine 100 mg PO bid/tid x 3-12 mo

Treatment of Alcohol Use Disorder
- non-pharmacological
  - psychotherapy: motivational enhancement therapy (MET; increasing motivation to change), CBT (assertiveness training, increasing social support, planning leisure activities), marital and family therapy
  - behavior therapy: contingency management, community reinforcement approach (CRA)
  - supportive services: counseling, detoxification centers, Alcoholics Anonymous
  - inpatient programs (e.g. 28-day programs)
    - individual readiness for change must always be considered with non-pharmacological interventions (see Prochaska's Stages of Change Model, Population Health and Epidemiology, PH6)
- pharmacological
  - naltrexone (Revia®): opioid antagonist, shown to be successful in reducing the “high” associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges
  - disulfiram (Antabuse®): blocks oxidation of alcohol (blocks acetaldehyde dehydrogenase); with alcohol consumption, acetaldehyde accumulates to cause a toxic reaction (vomiting, tachycardia, death); if patient relapses, must wait 48 h before restarting Antabuse®
  - acamprosate (Campral®): NMDA glutamate receptor antagonist; useful in maintaining abstinence and decreasing cravings
### Opioids

- **types of opioids**: heroin, morphine, oxycodone, Tylenol #3® (codeine), hydromorphone
- **major risks associated with the use of contaminated needles**: increased risk of hepatitis B and C, bacterial endocarditis, HIV/AIDS

### Acute Intoxication
- direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), and respiratory depression

### Toxic Reaction
- typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
- management
  - ABCs
  - IV glucose
  - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
- treatment: intubation and mechanical ventilation, ± naloxone drip, until patient alert without naloxone (>48 h with long-acting opioids)
- caution with longer half-life; may need to observe for toxic reaction for at least 24 h

### Withdrawal
- symptoms: depression, insomnia, drug-craving, myalgias, nausea, chills, autonomic instability (lacrimation, rhinorrhea, piloerection)
- onset: 6-12 h; duration: 5-10 d
- complications: loss of tolerance (overdose on relapse), miscarriage, premature labor
- management: long-acting oral opioids (methadone, buprenorphine), α-adrenergic agonists (clonidine)

### Treatment of Opioid Use Disorder
- psychosocial treatment (e.g. Narcotics Anonymous) usually emphasize total abstinence
- naltrexone or naloxone (opioid antagonists) may also be used to extinguish drug-seeking behavior
- long-term treatment may include withdrawal maintenance treatment with methadone or buprenorphine
- Suboxone® formulation includes naloxone in addition to buprenorphine, in an effort to prevent injection of the drug. When naloxone is injected, it will precipitate opiate withdrawal and block the opiate effect of buprenorphine, however it will not have this antagonist action when taken sublingually

### Cocaine

- **street names**: blow, C, coke, crack, flake, freebase, rock, snow
- **alkaloid extracted from leaves of the coca plant**: blocks presynaptic uptake of dopamine (causing euphoria), norepinephrine and epinephrine (causing vasospasm, HTN)
- **self-administered by inhalation or intravenous route**

### Intoxication
- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (e.g. tachycardia, mydriasis, sweating)
- prolonged use may result in paranoia and psychosis

### Overdose
- medical emergency: HTN, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias
- treatment with IV diazepam to control seizures and propanolol or labetalol to manage HTN and arrhythmias

### Withdrawal
- initial “crash” (1-48 h): increased sleep, increased appetite
- withdrawal (1-10 wk): dysphoric mood plus fatigue, irritability, vivid unpleasant dreams, insomnia or hypersomnia, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management

### Treatment of Cocaine Use Disorder
- psychotherapy, group therapy, NA, and behavior modification useful in maintaining abstinence

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### Opioid Antagonists: Naltrexone vs. Naloxone

- **Naltrexone (Revia®)**
  - Used for opioid and EtOH dependence
  - Long half life (h)
- **Naloxone (Narcan®)**
  - Used for life-threatening CNS/respiratory depression in opioid overdose
  - Short half life (<1 h)
  - Very fast acting (min)
  - High affinity for opioid receptor
  - Induces opioid withdrawal symptoms

---

### Common Presentations of Drug Use

<table>
<thead>
<tr>
<th>System</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Weight loss (especially cocaine, heroin)</td>
</tr>
<tr>
<td></td>
<td>Injected conjunctiva (cannabis)</td>
</tr>
<tr>
<td></td>
<td>Pinpoint pupils (opioids)</td>
</tr>
<tr>
<td></td>
<td>Track marks (injection drugs)</td>
</tr>
<tr>
<td>MSK</td>
<td>Trauma</td>
</tr>
<tr>
<td>GI</td>
<td>Viral hepatitis</td>
</tr>
<tr>
<td></td>
<td>Injection drugs</td>
</tr>
<tr>
<td></td>
<td>Unexplained elevations in ALT (injection drugs)</td>
</tr>
<tr>
<td>Behavioral</td>
<td>Missed appointments</td>
</tr>
<tr>
<td></td>
<td>Non-compliance</td>
</tr>
<tr>
<td></td>
<td>Drug-seeking (especially benzodiazepines, opioids)</td>
</tr>
<tr>
<td>Psychological</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Flat affect</td>
</tr>
<tr>
<td></td>
<td>(benzodiazepines, barbiturates)</td>
</tr>
<tr>
<td></td>
<td>Paranoia (cannabis)</td>
</tr>
<tr>
<td></td>
<td>Psychosis (cannabis, cannabis, hallucinogens)</td>
</tr>
<tr>
<td>Social</td>
<td>Marital discord</td>
</tr>
<tr>
<td></td>
<td>Family violence</td>
</tr>
<tr>
<td></td>
<td>Work/school</td>
</tr>
<tr>
<td></td>
<td>Absenteeism and poor performance</td>
</tr>
</tbody>
</table>
Complications
- cardiovascular: arrhythmias, MI, CVA, ruptured AAA
- neurologic: seizures
- psychiatric: psychosis, paranoia, delirium, suicidal ideation

Amphetamines
- intoxication characterized by euphoria, improved concentration, sympathetic and behavioral hyperactivity and at high doses can cause coma
- chronic use can produce a paranoid psychosis which can resemble schizophrenia with agitation, paranoia, delusions and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- treatment of stimulant psychosis: antipsychotics

Cannabis
- cannabis (marijuana) is the most commonly used illicit drug
- psychoactive substance: delta-9-tetrahydrocannabinol (δ9-THC)
- intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, altered sensorium, increased appetite, increased sense of well-being, euphoria/laughter, muscle relaxation, impaired performance on psychomotor tasks including driving
- high doses can cause depersonalization, paranoia, anxiety and may trigger psychosis and schizophrenia if predisposed
- chronic use associated with tolerance and an apathetic, amotivational state
- cessation does produce a significant withdrawal phenomenon
- treatment of cannabis use disorder: behavioral and psychological interventions to maintain an abstinence state

Hallucinogens
- types of hallucinogens: LSD, mescaline, psilocybin mushrooms, PCP, salvia
- LSD is a highly potent drug; intoxication characterized by tachycardia, HTN, mydriasis, tremor, hyperpyrexia, and a variety of perceptual and mood changes
- high doses can cause depersonalization, paranoia, and anxiety
- no specific withdrawal syndrome characterized
- treatment of agitation and psychosis: support, reassurance, diminished stimulation; benzodiazepines or high potency antipsychotics seldom required

Table 6. The Mechanism and Effects of Common “Club Drugs”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA (‘Ecstasy’, ‘X’, ‘E’)</td>
<td>Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and stimulant</td>
<td>Enhanced sensorium; feelings of well-being, empathy</td>
<td>Sweating, tachycardia-fatigue, muscle spasms (especially jaw clenching), ataxia, hyperthermia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death</td>
</tr>
<tr>
<td>Gamma Hydroxybutyrate (GHB, “G”, Liquid Ecstasy’)</td>
<td>Biphasic dopamine response (inhibition then release) and releases opiate-like substance</td>
<td>Euphoric effects, increased aggression, impaired judgment</td>
<td>Sweating, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, severe withdrawal from abrupt cessation of high doses: tremor, seizures, psychosis</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol®, “Roofies”, “Rope”, “The Forget Pill”)</td>
<td>Potent benzodiazepine, rapid oral absorption</td>
<td>Sedation, psychomotor impairment, amnestic effects, decreased sexual inhibition</td>
<td>CNS depression with EtOH</td>
</tr>
<tr>
<td>Ketamine (‘Special K’, ‘Kit-Kat’)</td>
<td>NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics and by veterinarians</td>
<td>“Dissociative” state, profound amnesia/ analgesia; hallucinations and sympathomimetic effects</td>
<td>Psychological distress, accidents due to intensity of experience and lack of bodily control, in overdose, decreased LOC, respiratory depression, catatonia</td>
</tr>
</tbody>
</table>

Date Rape Drugs
- GHB
- Flunitrazepam (Rohypnol®)
- Ketamine

Formication
Tactile hallucination that insects or snakes are crawling over or under the skin (especially associated with crystal meth use)

Pharm Party
An increasing trend among teenagers where assorted prescription medications are brought to a party and ingested at random

Medical Uses of Marijuana
- Anorexia-cachexia (AIDS, cancer)
- Spasticity, muscle spasms (multiple sclerosis, spinal cord injury)
- Levodopa-induced dyskinesia (Parkinson’s Disease)
- Controlling tics and obsessive-compulsive behavior (Tourette’s syndrome)
- Reducing intraocular pressure (glaucoma)

Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review
The Lancet 2007;370:319-328
Purpose: To review the evidence for cannabis use and occurrence of psychotic or affective mental health outcomes.
Study Characteristics: A meta-analysis of 35 population-based longitudinal studies, or case-control studies nested within longitudinal designs.
Results: There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio = 1.41, 95% CI 1.30-1.53). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently (2.09, 95% CI 1.54-2.84). Findings for depression, suicidal thoughts, and anxiety outcomes were less consistent. In both cases (psychotic and affective outcomes), a substantial confounding effect was present.
Conclusions: The findings are consistent with the view that cannabis increases risk of psychotic outcomes independent of transient intoxication effects, although evidence is less strong for affective outcomes. Although cannabis use and the development of psychosis are strongly associated, it is difficult to determine causality and it is possible that the association results from confounding factors or bias. The authors did conclude that there is sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.
Table 6. The Mechanism and Effects of Common "Club Drugs" (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methamphetamine</td>
<td>Amphetamine stimulant, induces norepinephrine, dopamine, and serotonin</td>
<td>Rush begins in min, effects last 6-8 h, increased activity, decreased</td>
<td>Short-term use: high agitation, rage, violent behavior, occasionally hyperthermia and convulsions</td>
</tr>
<tr>
<td>(&quot;speed&quot;, &quot;meth&quot;, &quot;chalk&quot;, &quot;ice&quot;, &quot;crystal&quot;)</td>
<td>release</td>
<td>appreciated, general sense of well-being, tolerance occurs quickly, users often binge and crash</td>
<td>Long-term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (especially formication), delusions, mood disturbance, suicidal and homicidal thoughts, stroke, may be contaminated with lead, and IV users may present with acute lead poisoning</td>
</tr>
<tr>
<td>Phencyclidine</td>
<td>Not understood, used by veterinarians to immobilize large animals</td>
<td>Amnestic, euphoric, hallucinatory state</td>
<td>High dose can cause coma</td>
</tr>
<tr>
<td>(&quot;PCP&quot;, &quot;angel dust&quot;)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Somatic Symptom and Related Disorders

General Characteristics
- physical signs and symptoms lacking a known medical basis in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance
- cause significant distress or impairment in functioning
- symptoms are produced unconsciously and are not the result of malingering or factitious disorder
- primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict with no external incentive
- secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (e.g. work)

Management of Somatic Symptom and Related Disorders
- brief frequent visits
- limit number of physicians involved in care
- focus on psychosocial not physical symptoms
- minimize medical investigations; coordinate necessary investigations
- psychotherapy: CBT, biofeedback, conflict resolution
- minimize psychotropic drugs: anxiolytics in short-term only, antidepressants for depressive and anxiety symptoms

Somatic Symptom Disorder

DSM-5 Diagnostic Criteria for Somatic Symptom Disorder
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. one or more somatic symptoms that are distressing or result in significant disruption of daily life
B. excessive thoughts, feelings, or behaviors related to the somatic symptoms or associated health concerns as manifested by at least one of the following
   1. disproportionate and persistent thoughts about the seriousness of one's symptoms
   2. persistently high level of anxiety about health or symptoms
   3. excessive time and energy devoted to these symptoms or health concerns
C. although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 mo)

- symptoms may or may not be associated with another medical condition
- lifetime prevalence may be around 5-7% in the general adult population
- females tend to report more somatic symptoms than males do, cultural factors may influence sex ratio
- complications: anxiety, depression, unnecessary medications or surgery
- often a misdiagnosis for an insidious illness so rule out all organic illnesses (e.g. multiple sclerosis)
Illness Anxiety Disorder (formerly Hypochondriasis)

- preoccupation with fear of having, or the idea that one has, a serious disease based on a misinterpretation of one or more bodily signs or symptoms
- evidence does not support diagnosis of a physical disorder
- fear of having a disease despite medical reassurance
- belief is not of delusional intensity (as in delusional disorder, somatic type) as person acknowledges unrealistic interpretation
- duration is ≥6 mo; onset in 3rd-4th decade of life
- community prevalence 1.1-4.5%; prevalence in general medical practice 4-9%; higher in psychiatric settings
- role for SSRIs due to anxiety

Conversion Disorder

(Functional Neurological Symptom Disorder)

- one or more symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or GMC (e.g. impaired co-ordination, local paralysis, double vision, seizures, or convulsions)
- does not need to be preceded by a psychological event as per previous DSM criteria
- 2-5/100,000 in general population; 5% of referrals to neurology clinics
- more common in rural populations and in individuals with little medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 mo)

Dissociative Disorders

Definition

- dissociation so severe that the usually integrated functions of consciousness and perception of self break down
- sudden or gradual onset, transient or chronic course
- symptoms cause distress or impaired functioning
- differential diagnosis: PTSD, acute stress disorder, somatization disorder, substance abuse, GMC (e.g. complex/partial seizures)

Table 7. Dissociative Disorders

<table>
<thead>
<tr>
<th>Amnesia</th>
<th>Fugue</th>
<th>Identity Disorder</th>
<th>Depersonalization/Derealization Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>Amnesia</td>
<td>Identity Disorder</td>
<td>Depersonalization/Derealization Disorder</td>
</tr>
<tr>
<td>Inability to recall important personal information, usually of a traumatic or stressful nature, may be localized, selective, or generalized</td>
<td>Sudden, unexpected travel away from home or workplace with inability to recall some or all of one’s past; may assume new identity</td>
<td>Two or more distinct personalities that take control of an individual’s behavior; amnesia regarding personal history (i.e. Multiple Personality Disorder)</td>
<td>Persistent or recurrent experiences of feeling detached from one’s mental processes or body (i.e. like being in a dream)</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>6% prevalence</td>
<td>0.2% prevalence</td>
<td>1.3% prevalence, M:F=1:3:9</td>
</tr>
<tr>
<td>Increased in survivors of trauma (war, abuse)</td>
<td>May occur under traumatic circumstances (combat, rape, natural disasters)</td>
<td>May have history of physical or sexual abuse</td>
<td>Rare disorder</td>
</tr>
<tr>
<td>Treatment</td>
<td>Psychotherapy, hypnosis</td>
<td>Usually spontaneous recovery</td>
<td>Three stages: symptom stabilization, attention to trauma, reintegration</td>
</tr>
<tr>
<td>No proven role for barbiturates/pharmacologically-assisted interviewing</td>
<td>Psychotherapy, hypnosis</td>
<td>Psychotherapy, hypnosis</td>
<td>Psychotherapy, hypnosis</td>
</tr>
<tr>
<td>Ensure stability and safety</td>
<td>Ensure stability and safety</td>
<td>Symptom-oriented adjuvants</td>
<td>Hypnosis</td>
</tr>
<tr>
<td>No proven role for barbiturates/pharmacologically-assisted interviewing</td>
<td>No proven role for barbiturates/pharmacologically-assisted interviewing</td>
<td>(antidepressants, anxiolytics)</td>
<td>No proven role for barbiturates/pharmacologically-assisted interviewing</td>
</tr>
<tr>
<td>Treatment</td>
<td>Psychotherapy</td>
<td>Three stages: symptom stabilization, attention to trauma, reintegration</td>
<td>Psychotherapy</td>
</tr>
<tr>
<td>Pharmacotherapy: clonazepam, fluoxetine, clomipramine</td>
<td>Pharmacotherapy: clonazepam, fluoxetine, clomipramine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sleep Disorders

- see Neurology, N45

Criteria for Diagnosis

- causes significant distress or impairment in functioning
- not due to medications, drugs, or a GMC
**Nocturnal Myoclonus**

- middle-aged and elderly
- myoclonic jerks every 20-40 s
- bed partner complaints
- treatment: benzodiazepines (clonazepam, nitrazepam)

**Narcolepsy**

- see Neurology, N47

**Primary Insomnia**

- see Family Medicine, FM47

**Sleep Apnea**

- see Respirology, R31

**Sexuality and Gender**

**Gender Dysphoria**

- refers to the distress that may coincide with conflict between one’s experienced/expressed gender and one’s assigned gender
- **typical presentation**
  - strong and persistent cross-gender identification
  - desire to be rid of primary/secondary sex characteristics and to gain the primary/secondary sex characteristics of their identified gender
  - repeated stated desire or insistence that one is of the opposite sex
  - preference for cross-dressing, cross-gender roles in make-believe play
  - intense desire to participate in the stereotypical games and pastimes of the opposite sex
  - strong preference for playmates of the opposite sex
  - significant distress or impairment in functioning and persistent discomfort with his or her sex or gender role
- **treatment**
  - psychotherapy
  - hormonal therapy
  - sexual reassignment surgery

**Paraphilic Disorders**

- **definition**: intense and persistent sexual interest other than sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners
- **paraphilic disorder**: paraphilia that causes distress or functional impairment to the individual, or a paraphilia whose realization entails personal harm, or risk of harm to others
- subtypes: voyeuristic, exhibitionistic, frotteuristic, sexual masochism, sexual sadism, pedophilic, fetishistic, transvestic, other specified paraphilic disorder, unspecified paraphilic disorder
- rarely self-referred; come to medical attention through interpersonal or legal conflict
- person usually has more than one paraphilia; 5% of paraphilias attributed to women
- **typical presentation**
  - begins in childhood or early adolescence; increasing in complexity and stability with age
  - chronic, decreases with advancing age but may increase with stress
- **treatment**
  - anti-androgen drugs
  - behavior modification
  - psychotherapy

**SEXUAL DYSFUNCTION**

- see Gynecology, GY30 and Urology, U30
Eating Disorders

Epidemiology
• anorexia nervosa (AN): 1% of adolescent and young adult females; onset 13-20 yr old
• bulimia nervosa (BN): 2-4% of adolescent and young adult females; onset 16-18 yr old
• F:M=10:1; mortality 5-10%

Etiology
• multifactorial: psychological, sociological, and biological associations
• individual: perfectionism, lack of control in other life areas, history of sexual abuse
• personality: obsessive-compulsive, histrionic, borderline
• familial: maintenance of weight equilibrium and control in dysfunctional family
• cultural factors: prevalent in industrialized societies, idealization of thinness in the media
• genetic factors
  ▪ AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs vs. concordance in 1 of 14 dizygotic pairs
  ▪ BN: higher familial incidence of affective disorders than the general population

Risk Factors
• physical factors: obesity, chronic medical illness (e.g. DM)
• psychological factors: individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance abuse), history of sexual abuse, homosexual males, competitive athletes, concurrent associated mental illness (depression, OCD, anxiety disorder [especially panic and agoraphobia], substance abuse [specifically for BN])

Anorexia Nervosa

DSM-5 Diagnostic Criteria for Anorexia Nervosa
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected
B. intense fear of gaining weight or of becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight
C. disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight
• specifiers: partial remission, full remission, severity based on BMI (mild = BMI >17 kg/m², moderate = BMI 16-16.99 kg/m², severe = BMI 15-15.99 kg/m², extreme = BMI <15 kg/m²), type (restricting = during last 3 mo no episodes of binge-eating or purging vs. binge-eating/purging type = in last 3 mo have participated in recurrent episodes of binge-eating/purging)

Management
• outpatient programs and inpatient programs are available
• inpatient hospitalization for treatment of eating disorders is rarely on an acute basis (unless there is a concurrent psychiatric reason for emergent admission e.g. suicide risk)
• admit to a medical ward for hospitalization: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry or if actively suicidal
• agree on target body weight on admission and reassure this weight will not be surpassed
• psychotherapy (individual/group/family): address food and body perception, coping mechanisms, health effects
• monitor for complications of AN (see Table 8)
• monitor for refeeding syndrome
  ▪ a potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
  ▪ complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium, and death
  ▪ prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, close monitoring of electrolytes and cardiac status

Athletic Triad
• Disordered eating
• Amenorrhea
• Osteoporosis

Some patients with insulin-dependant diabetes mellitus may stop their insulin in order to lose weight
Prognosis
- early intervention much more effective (adolescent onset has much better prognosis than adult onset)
- 1 in 10 adolescents continue to have anorexia nervosa as adults
- with treatment, 70% resume a weight of at least 85% of expected levels and about 50% resume normal menstrual function
- eating peculiarities and associated psychiatric symptoms are common and persistent
- long-term mortality: 10-20% of patients hospitalized will die in next 10-30 yr (secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion committing suicide)

Bulimia Nervosa

DSM-5 Diagnostic Criteria for Bulimia Nervosa
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. recurrent episodes of binge-eating; an episode of binge-eating is characterized by both of the following
   - eating, in a discrete period of time, an amount of food that is definitely larger than what most individuals would eat during a similar period of time and under similar circumstances
   - a sense of lack of control over eating during the episode
B. recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise
C. the binge-eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo
D. self-evaluation is unduly influenced by body shape and weight
E. the disturbance does not occur exclusively during episodes of AN
   • specifiers: partial remission, full remission, severity (mild = 1-3 inappropriate compensatory behaviors/wk, moderate = 4-7 inappropriate compensatory behaviors/wk, severe = 8-13 inappropriate compensatory behaviors/wk, extreme = 14+ inappropriate compensatory behaviors/wk)

Associated Features
- fatigue and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
- tooth decay
- swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention
- reddened knuckles, Russell's sign (knuckle callus from self-induced vomiting)
- trouble concentrating
- weight fluctuation over time

Management
- admission for significant electrolyte abnormalities
- biological: treatment of starvation effects, SSRIs
- psychological: develop trusting relationship with therapist to explore personal etiology and triggers, CBT, family therapy, recognition of health risks
- social: challenge destructive societal views of women, use of hospital environment to provide external patterning for normative eating behavior

Prognosis
- relapsing/remitting disease
- good prognostic factors: onset before age 15, achieving a healthy weight within 2 yr of treatment
- poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance
- 60% good treatment outcome, 30% intermediate outcome, 10% poor outcome

Avoidant/Restrictive Food Intake Disorder
- definition: eating/feeding disturbance to the point that there is persistent failure to meet appropriate nutritional and/or energy needs such that individual experiences significant weight loss/growth failure, have nutritional deficiencies, may become dependent on enteral feeding/oral nutritional supplementation, has a marked interference with psychosocial functioning
- risk factors: temperament (e.g. anxiety disorders), environment (e.g. familial anxiety), genetic (e.g. history of GI conditions)
- begins in infancy and can persist into adulthood
- treatment
  - watchful waiting
  - behavior modification
  - psychotherapy
**Binge-Eating Disorder**

- **definition:** recurrent episodes of binge-eating (as defined by criteria A of BN) that are associated with eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts when not physically hungry, eating alone because embarrassed by how much one is eating, feeling disgusted with oneself/depressed/very guilty afterwards at least once/wk x 3 mo
- not associated with any compensatory behaviors
- dieting usually follows binge-eating (vs. BN where dysfunctional dieting typically precedes binge-eating)
- **epidemiology:** F:M = 2:1
- associated with health consequences (e.g. increased risk of weight gain, obesity)
- begins in adolescence or young-adulthood
- hallmark of treatment is CBT

<table>
<thead>
<tr>
<th>Table 8. Physiologic Complications of Eating Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>System</strong></td>
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<tr>
<td>------------</td>
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<tr>
<td><strong>General</strong></td>
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<tr>
<td><strong>Endocrine</strong></td>
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<tr>
<td><strong>Neurologic</strong></td>
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<tr>
<td><strong>Cutaneous</strong></td>
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<tr>
<td><strong>GI</strong></td>
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<tr>
<td><strong>CVS</strong></td>
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<tr>
<td><strong>MSK</strong></td>
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<tr>
<td><strong>Renal</strong></td>
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<tr>
<td><strong>Extremities</strong></td>
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<tr>
<td><strong>Lab Values</strong></td>
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</tbody>
</table>

**Personality Disorders**

- an evolving personality disorder literature describes that personality is better understood using a trait-based dimensional approach rather than discrete categories, however the discrete categories still remain in the current DSM and will be referenced here

**General Diagnostic Criteria**

- an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- pattern is stable and well established by adolescence or early adulthood
- associated with many complications, such as depression, suicide, violence, brief psychotic episodes, multiple drug use, and treatment resistance
- the mainstay of treatment is psychotherapy with the addition of pharmacotherapy to treat associated axis I disorders (i.e. depression, anxiety, substance abuse)
- main treatment for borderline personality disorder is dialectical behavioral therapy (consists of validating rather than blaming the patient, and replacing maladaptive behavior with adaptive behavior)
Table 9. Classification and Diagnosis of Personality Disorders

Note: For each personality disorder, the most recognizable feature is indicated in italics.

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Paraphrenic Personality Disorder (0.5-3%)</th>
<th>Schizotypal Personality Disorder (3-5.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster A “Mad”</td>
<td>Paranoid Personality Disorder</td>
<td>Schizotypal Personality Disorder</td>
</tr>
<tr>
<td></td>
<td>Patients seem odd, eccentric, withdrawn</td>
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<tr>
<td></td>
<td>Familial association with psychotic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disorders</td>
<td></td>
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<tr>
<td></td>
<td>Common defense mechanisms:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>intellectualization, projection, magical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>thinking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 4 of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Suspicious that others are exploiting</td>
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</tr>
<tr>
<td></td>
<td>or deceiving them</td>
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</tr>
<tr>
<td></td>
<td>2. Pre-occupied with trustworthiness of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>acquaintances</td>
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</tr>
<tr>
<td></td>
<td>3. Reluctant to confide in others</td>
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<td></td>
<td>4. Interpret benign remarks as threatening,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>demeaning</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Holds grudges</td>
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<td></td>
<td>6. Perceives attacks on character and is</td>
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<tr>
<td></td>
<td>quick to counterattack</td>
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<tr>
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<td>7. Questions fidelity of partner without</td>
<td></td>
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<td></td>
<td>justification</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schizoid Personality Disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neither desires nor enjoys close</td>
<td></td>
</tr>
<tr>
<td></td>
<td>relationships including being a part of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a family; prefers to be alone.</td>
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</tr>
<tr>
<td></td>
<td>Lifelong pattern of social withdrawal.</td>
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<tr>
<td></td>
<td>Diagnosis requires 4 of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Does not enjoy or desire close</td>
<td></td>
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<tr>
<td></td>
<td>relationships</td>
<td></td>
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<tr>
<td></td>
<td>2. Chooses solitary activities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Little to no interest in sexual</td>
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</tr>
<tr>
<td></td>
<td>activity with others</td>
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</tr>
<tr>
<td></td>
<td>4. Takes pleasure in few (if any)</td>
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</tr>
<tr>
<td></td>
<td>activities</td>
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</tr>
<tr>
<td></td>
<td>5. Few or no close friends</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Indifference to praise or criticism</td>
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</tr>
<tr>
<td></td>
<td>7. Emotionally cold, detached, or has</td>
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<tr>
<td></td>
<td>flattened affect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cluster B “Bad”</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patients seem dramatic, emotional,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>inconsistent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Familial association with mood disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common defense mechanisms:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>denial, acting out, regression (histrionic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PD), splitting (borderline PD), projective</td>
<td></td>
</tr>
<tr>
<td></td>
<td>identification, idealization/devaluation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline Personality Disorder (2-4%)</td>
<td>Narcissistic Personality Disorder (2%)</td>
</tr>
<tr>
<td></td>
<td>Unstable moods and behavior; feel alone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in the world, problems with self image.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>History of repeated suicide attempts,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>self-harm behaviors.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>10% suicide rate</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 5 of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Frantic efforts to avoid real or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>imagined abandonment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Unstable and intense relationships</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Unstable sense of self</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Impulsivity in two potentially</td>
<td></td>
</tr>
<tr>
<td></td>
<td>harmful ways (sexual, drugs, spending)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Recurrent suicidal behavior/self-harm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Unstable mood/affect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. General feelings of emptiness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. Difficulty controlling anger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9. Transient dissociative symptoms or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paranoid ideation associated with stress</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antisocial Personality Disorder (M: 3%,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F: 1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lack of remorse for actions, manipulative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and deceitful, often violate the law.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May appear charming on first impression.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pattern of disregard for others and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>violation of rights of others must be</td>
<td></td>
</tr>
<tr>
<td></td>
<td>present before the age of 15; however,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>for the diagnosis of ASPD patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>must be at least 18.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 3 of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Failure to conform to social norms by</td>
<td></td>
</tr>
<tr>
<td></td>
<td>committing unlawful acts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Deceitfulness, lying, manipulating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>others for personal gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Impulsive, fails to plan ahead</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Irritable, aggressive, repeated fights</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or assaults</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Recklessness and disregard for</td>
<td></td>
</tr>
<tr>
<td></td>
<td>personal safety; safety of others</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Irresponsible, cannot sustain work</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Lack of remorse for actions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Histrionic Personality Disorder (1.3-3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Attention-seeking behavior and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>excessively emotional. Are</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dramatic, flamboyant, and extroverted.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cannot form meaningful relationships.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often sexually inappropriate.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 5 of:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Not comfortable unless center of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>attention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Inappropriately sexually seductive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Uses physical appearance to attract</td>
<td></td>
</tr>
<tr>
<td></td>
<td>attention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Speech is impressionistic, lacks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>detail</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Theatrical and exaggerated expression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of emotion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6. Easily influenced by others</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Perceives relationships as more</td>
<td></td>
</tr>
<tr>
<td></td>
<td>intimate than they actually are</td>
<td></td>
</tr>
</tbody>
</table>
Table 9. Classification and Diagnosis of Personality Disorders (continued)

<table>
<thead>
<tr>
<th>Diagnostic Cluster</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster C “Sad”</td>
<td>Avoidant Personality Disorder (0.5-1.6%)</td>
</tr>
<tr>
<td></td>
<td>Tidly and socially awkward with a pervasive sense of inadequacy and fear of criticism. Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited.</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 4 of:</td>
</tr>
<tr>
<td></td>
<td>1. Avoids occupational activities that involve significant interpersonal contact for fear of criticism or rejection</td>
</tr>
<tr>
<td></td>
<td>2. Unwilling to get involved with people unless certain of being liked</td>
</tr>
<tr>
<td></td>
<td>3. Restrained in intimate relationships for fear of being shamed or ridiculed</td>
</tr>
<tr>
<td></td>
<td>4. Preoccupied with being rejected or criticized in social situations</td>
</tr>
<tr>
<td></td>
<td>5. Inhibited in new interpersonal situations due to fear of inadequacy</td>
</tr>
<tr>
<td></td>
<td>6. Views him or herself as inferior, socially inept or personally unappealing</td>
</tr>
<tr>
<td></td>
<td>7. Reluctant to engage in new activities for fear of embarrassment</td>
</tr>
<tr>
<td>Dependent Personality Disorder (1.6-6.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviors. Difficulty making everyday decisions.</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 5 of:</td>
</tr>
<tr>
<td></td>
<td>1. Difficulty making everyday decisions without advice and reassurance from others</td>
</tr>
<tr>
<td></td>
<td>2. Needs others to assume responsibility for most major areas of his/her life</td>
</tr>
<tr>
<td></td>
<td>3. Difficulty expressing disagreement</td>
</tr>
<tr>
<td></td>
<td>4. Difficulty initiating projects due to lack of self-confidence</td>
</tr>
<tr>
<td></td>
<td>5. Goes to excessive lengths to obtain support</td>
</tr>
<tr>
<td></td>
<td>6. Uncomfortable or helpless when alone because of fear of being unable to take care of him/herself</td>
</tr>
<tr>
<td></td>
<td>7. Urgently seeks another relationship as a source of care and support when a close relationship ends</td>
</tr>
<tr>
<td></td>
<td>8. Unrealistically preoccupied with fears of being left to take care of him/herself</td>
</tr>
<tr>
<td>Obsessive-Compulsive Personality Disorder (3-10%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Preoccupation with orderliness, perfectionism, and mental and interpersonal control. Is inflexible, closed-off, and inefficient.</td>
</tr>
<tr>
<td></td>
<td>Diagnosis requires 4 of:</td>
</tr>
<tr>
<td></td>
<td>1. Preoccupation with details, rules, lists, order, organization, or schedules to the extent that the point of an activity is lost</td>
</tr>
<tr>
<td></td>
<td>2. Perfectionism interferes with task completion</td>
</tr>
<tr>
<td></td>
<td>3. Excessively devoted to work the exclusion of leisure activities and friendships</td>
</tr>
<tr>
<td></td>
<td>4. Inflexible about morality/ethics/values</td>
</tr>
<tr>
<td></td>
<td>5. Unable to discard worthless objects of no sentimental value</td>
</tr>
<tr>
<td></td>
<td>6. Reluctant to delegate tasks to others</td>
</tr>
<tr>
<td></td>
<td>7. Misery spending style (money is hoarded for future disasters)</td>
</tr>
<tr>
<td></td>
<td>8. Rigid and stubborn</td>
</tr>
</tbody>
</table>

Table 10. Key Differences Among Schizoid, Schizotypal, and Schizophrenia

<table>
<thead>
<tr>
<th>Schizoid</th>
<th>Schizotypal</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thought Form</td>
<td>Organized</td>
<td>Organized, but vague and circumstantial</td>
</tr>
<tr>
<td>Thought Content</td>
<td>No psychosis</td>
<td>No psychosis, may have ideas of reference, paranoid ideation, odd beliefs and magical thinking</td>
</tr>
<tr>
<td>Relationships</td>
<td>Solitary, NO desire for social relationships</td>
<td>Lacks close relationships, INTERESTED in relationships but socially inept</td>
</tr>
</tbody>
</table>

Child Psychiatry

Developmental Concepts

- **temperament**: innate psycho-physiological and behavioral characteristics of a child (e.g. emotionality, activity, and sociability); spectrum from “difficult” to “slow-to-warm-up” to “easy temperament”
- **parental fit**: the congruence between parenting style (authoritative, authoritarian, permissive) and child’s temperament
- **attachment**: special relationship between child and primary caretaker(s); develops during first year, best predictor of a child’s attachment style is their parent’s attachment style
- **separation anxiety** (10-18 mo): separation from attachment figure results in distress
Table 11. Attachment Models

<table>
<thead>
<tr>
<th>Parent/Caregiver</th>
<th>Attachment Type</th>
<th>Features in Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loving, consistently available, sensitive, and</td>
<td>Secure</td>
<td>Able to use caregiver to calm self</td>
</tr>
<tr>
<td>receive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rejecting, unavailable psychologically, insensitive</td>
<td>Insecure (avoidant)</td>
<td>Not reliant on caregiver for soothing</td>
</tr>
<tr>
<td>responses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inconsistent, insensitive responses, role reversal</td>
<td>Insecure (ambivalent/resistant)</td>
<td></td>
</tr>
<tr>
<td>Frightening, dissociated, sexualized, or atypical</td>
<td>Disorganized</td>
<td></td>
</tr>
</tbody>
</table>

**Mood Disorders**

**MAJOR DEPRESSIVE DISORDER**

**Epidemiology**
- pre-pubertal 1-2% (no gender differences); post-pubertal 4-18% (F:M = 2:1)

**Clinical Presentation**
- see Adult Mood Disorders, PS6
- physical factors: insomnia (children), hypersomnia (adolescents), somatic complaints, substance abuse
- psychological factors: irritability, boredom, anhedonia, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation
- comorbid diagnoses of anxiety, ADHD, conduct disorder, and eating disorders

**Treatment**
- majority never seek treatment
- individual (CBT, IPT)/family therapy and education, modified school program
- SSRIs (strongest evidence for fluoxetine)
- ECT: only in adolescents

**Prognosis**
- prolonged episodes, up to 1-2 yr
- adolescent onset predicts chronic mood disorder; up to 2/3 will have another depressive episode within 5 yr
- complications
  - negative impact on family and peer relationships
  - school failure
  - significantly increased risk of suicide attempt (10%) or completion (however suicide risk low for pre-pubertal children)
  - substance abuse

**BIPOLAR DISORDER**

**Clinical Presentation**
- see Bipolar Disorder, PS9
- mixed presentation and psychotic symptoms (hallucinations and delusions) more common in adolescent population than adult population
- unipolar depression may be an early sign of adult bipolar disorder
  - ~30% of psychotic depressed adolescents receive a bipolar diagnosis within 2 yr of presentation
  - associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family, pharmacologically-induced mania

**Treatment**
- 1st line: mood stabilizers and/or antipsychotics
- 2nd line: antidepressants, benzodiazepines (careful of disinhibiting effect)

**Anxiety Disorders**

- prevalence 2-15%; F:M = 2:1

**Clinical Presentation**
- school problems, recurrent physical symptoms (abdominal pain, headaches) especially in mornings, social and relationship problems, social withdrawal and isolation, family conflict, irritability and mood symptoms, alcohol and drug use in adolescent
Treatment
• family psychotherapy, predictive and supportive environment
• CBT: child and parental education, relaxation techniques (e.g. deep breathing), exposure/desensitization, recognizing and correcting anxious thoughts
• pharmacotherapy: SSRIs (e.g. fluoxetine), benzodiazepines (e.g. clonazepam – use with caution, may have disinhibiting effect)
  ▪ fluvoxamine and sertraline also have good evidence, particularly for OCD

SEPARATION ANXIETY DISORDER

Epidemiology
• prevalence: 4% of children/adolescents
• average onset is 7.5 yr old; average age at presentation is 10 yr old
• common for mother to have an anxiety or depressive disorder

Differential Diagnosis
• simple or social phobia, depression, learning disorder, truancy, conduct disorder, school-related problems (e.g. bullying)

Clinical Presentation
• excessive and developmentally inappropriate anxiety on separation from primary caregiver with physical or emotional distress for at least 4 wk
• school refusal (75%)
• persistent worry, refusal to sleep, clinging, nightmares, somatic symptoms
• comorbid major depression common (2/3)
• worry about something happening to parent or themselves if separated

Prognosis
• if inadequately treated early on, may present later in a more severe form
• may develop into panic disorder with/without agoraphobia

SOCIAL PHOBIA (SOCIAL ANXIETY DISORDER)

• must distinguish between shy child and child with social anxiety
  ▪ diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning, or if markedly distressed
• features: temper tantrums, freezing, clinging behavior, mutism, excessively timid, stays on periphery, refuses to be involved in group play
• must be capable of developing social relationships
• must occur in settings with peers, not just adults

SELECTIVE MUTISM
• consistent failure to speak in specific social situations in which there is an expectation for speaking despite speaking in other situations
• the disturbance interferes with educational or occupational achievement or with social communication

PANIC DISORDER
• diagnostic criteria same as adults (see Panic Disorder, PS10)
• genetic/parental modeling/identification hypothesized as cause
• often parent with panic or depressive disorder

GENERALIZED ANXIETY DISORDER
• diagnostic criteria same as adults (see Generalized Anxiety Disorder, PS12)
  ▪ Note: only 1 item is required in children for Criteria C
• often redo tasks, show dissatisfaction with their work, and tend to be perfectionistic
• often require reassurance and support to take on new tasks

SPECIFIC PHOBIA
• common phobias in childhood include a fear of heights, small animals, doctors, dentists, darkness, loud noises, thunder and lightning
Neurodevelopmental Disorders

Autism Spectrum Disorder

- M:F = 3–4:1 (except for Rett’s with female predominance)

Diagnosis
- persistent deficits in social communication and interaction, manifested in three areas
  - social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation, to reduced sharing of interests, emotions, or affect, to failure to initiate or respond to social interactions
  - nonverbal communicative behaviors, ranging, for example, from poorly integrated verbal and nonverbal communication, to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to a total lack of facial expressions and nonverbal communication
  - developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends, to absence of interest in peers
- restricted, repetitive patterns of behavior, interests, or activities. Two or more of: stereotyped or repetitive motor movements, insistence on sameness, highly restricted fixedated interests, hyper/hypo-reactivity to sensory input
- symptoms must be present in early developmental period
- symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
- not better explained by intellectual disability or global developmental delay

- specifiers
  - current severity: requiring very substantial support, requiring substantial support, requiring support
  - with or without accompanying language impairment
  - with or without accompanying intellectual impairment
  - associated with known medical or genetic condition or environmental factors (i.e. Rett’s disorder)

Differential Diagnosis
- developmental disability, childhood schizophrenia, social phobia, OCD, communication disorder, non-verbal learning disorder, ADHD, abuse, hearing or visual impairment, seizure disorder, motor impairment

Management
- hearing test to rule out impairment
- psychological testing to assess intellectual functioning and learning
- chromosomal analysis to rule out abnormalities (e.g. Trisomy 21, Fragile X syndrome)
- rule out psychotic disorders, social problems, depression, anxiety, abuse

Treatment
- team-based: school, psychologist, occupational therapist, physiotherapist, speech and language therapy, audiology, pediatrics, psychiatry
- family education and support
- treat concomitant disorders such as tics, OCD, anxiety, depression, and seizure disorder
- behavior management, school programming
- pharmacotherapy: atypical antipsychotics (for aggression, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated inattention and hyperactivity)

Prognosis
- variable, but improves with early intervention
- better if IQ >60 and able to communicate

Attention Deficit Hyperactivity Disorder

- prevalence: 5–12% of school-aged children; M:F = 4:1, although girls may be under-diagnosed
- girls tend to have inattentive/distractible symptoms; boys have impulsive/hyperactive symptoms

Etiology
- genetic: dopamine candidate genes, catecholamine/neuroanatomical hypothesis
- cognitive: developmental disability, inhibitory control and other errors of executive function
- arousal: alterations in the sensory system filters
Diagnosis
- differential: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (fetal alcohol syndrome, Fragile X), lead poisoning, history of head injury, traumatic life events (abuse)
- diagnosis (3 subtypes)
  - **Combined Type**: 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity-impulsivity
  - **Predominantly Inattentive Type**: 6 or more symptoms of inattention
  - **Predominantly Hyperactive-Impulsive Type**: 6 or more symptoms of hyperactivity-impulsivity
- for older adolescents (>17 yr) or adults, 5 symptoms required
- symptoms persist for >6 mo
- onset before age 12
- symptoms present in at least two settings (i.e. home, school, work)
- interferes with academic, family, and social functioning
- does not occur exclusively during the course of another psychiatric disorder

Table 12. Core Symptoms of ADHD (DSM-5)

<table>
<thead>
<tr>
<th>Inattention</th>
<th>Hyperactivity</th>
<th>Impulsivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careless mistakes</td>
<td>Fidgets, squirms in seat</td>
<td>Blurs out answers before questions completed</td>
</tr>
<tr>
<td>Cannot sustain attention in tasks or play</td>
<td>Leaves seat when expected to remain seated</td>
<td>Difficulty awaiting turn</td>
</tr>
<tr>
<td>Does not listen when spoken to directly</td>
<td>Runs and climbs excessively</td>
<td>Interrupts/intrudes on others</td>
</tr>
<tr>
<td>Fails to complete tasks</td>
<td>Cannot play quietly</td>
<td></td>
</tr>
<tr>
<td>Disorganized</td>
<td>“On the go”, driven by a motor</td>
<td></td>
</tr>
<tr>
<td>Avoids, dislikes tasks that require sustained mental effort</td>
<td>Talks excessively</td>
<td></td>
</tr>
<tr>
<td>Loses things necessary for tasks or activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distractible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forgetful</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Features
- average onset 3 yr old
- identification upon school entry
- rule out developmental delay, genetic syndromes, encephalopathies or toxins (alcohol, lead)
- risk of substance abuse, particularly cannabis and cocaine, depression, anxiety, academic failure, poor social skills, risk of comorbid CD and/or ODD, risk of adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics

Treatment
- non-pharmacological: parent management, anger control strategies, positive reinforcement, social skills training, individual/family therapy, resource room, tutors, classroom intervention, exercise routines, extracurricular activities
- pharmacological
  - standard treatment
    - stimulants: methylphenidates (Ritalin*, Concerta® [long-acting]), Biphetin®
    - amphetamines: dextroamphetamine, mixed amphetamine salts (Adderall®), lisdexamfetamine (Vyvanse®)
    - SNRI: atomoxetine (Strattera®)
  - for comorbid symptoms: antidepressants, antipsychotics

Prognosis
- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable
- 70-80% continue into adolescence, but hyperactive symptoms usually abate
Disruptive, Impulse Control, and Conduct Disorder

Oppositional Defiant Disorder

- prevalence: 2-16%

Diagnosis

- pattern of negativistic/hostile and defiant behavior for ≥6 mo with ≥4 of
  - loses temper, argues with adults, defies adult rules, deliberately annoys, blames others, touchy/easily annoyed, angry and resentful, spiteful or vindictive
  - behavior causes significant impairment in social, academic, or occupational functioning
  - behaviors do not occur exclusively during the course of a psychotic or mood disorder
  - criteria not met for conduct disorder (CD); if 18 yr or older, criteria not met for ASPD
  - features that typically differentiate ODD from transient developmental stage: onset <8 yr, chronic duration (>6 mo), frequent intrusive behavior
  - impact of ODD: poor school performance, few friends, strained parent/child relationships
  - may progress to CD

Treatment

- establish boundaries
- parent management training and psychoeducation
- individual/family therapy
- pharmacotherapy for comorbid disorders
- school/day care interventions to help with behavior management

Conduct Disorder

- prevalence: 1.5-3.4% (M:F = 4-12:1)

Etiology

- parental/familial factors: parental psychopathology (e.g. ASPD, substance abuse), child-rearing practices (e.g. child abuse, discipline), low socio-economic status (SES), family violence
- child factors: difficult temperament, ODD, learning problems, neurobiology

Diagnosis

- differential: ADHD, depression, head injury, substance abuse
- diagnosis: use multiple sources (Achenbach Child Behavioral Checklist, Teacher's Report Form)
  - pattern of behavior that violates rights of others and age appropriate social norms with ≥3 criteria noted in past 12 mo and ≥1 in past 6 mo
    - aggression to people and animals (bullying, physical fights, use of weapons, forced sex)
    - destruction of property, firesetting with intent to damage
    - deceitfulness or theft (breaking and entering, car theft)
    - violation of rules (out all night before age 13, runaway ≥2 times or for long periods of time, often truant from school before age 13)
  - disturbance causes clinically significant impairment in social, academic, or occupational functioning
  - if individual is 18 yr or older, criteria not met for ASPD
  - diagnostic types
    - childhood onset: at least one criterion prior to age 10
      - poor prognosis: associated with ODD, aggressiveness, impulsiveness
    - adolescent onset: absence of any criteria until age 10
      - better prognosis; least aggressive, gang-related delinquency
    - mild, moderate, severe

Treatment

- early intervention necessary and more effective; long-term follow-up required
- parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training, medications for aggressiveness or comorbid disorders
- pharmacotherapy is insufficient; mainly used for treatment of comorbid disorders

Prognosis

- poor prognostic indicators include early-age onset, high frequency and variety of behaviors, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance abuse
- 50% of CD children become adult ASPD
Pharmacotherapy

Antipsychotics

- “antipsychotics” and “neuroleptics” are terms used interchangeably
- **indications**: schizophrenia and other psychotic disorders, mood disorders with or without psychosis, violent behavior, autism, Tourette’s, dementia, OCD
- **onset**: immediate calming effect and decrease in agitation; thought disorder responds in 2-4 wk
- **rational use**
  - no reason to combine antipsychotics
  - choosing an antipsychotic
    - all antipsychotics are equally effective, except for clozapine (considered to be most effective in treatment-refractory psychosis)
    - atypical antipsychotics are as effective as typical or first generation antipsychotics but are thought to have better side effect profiles
    - choose a drug that the patient has responded to in the past or that was used successfully in a family member
  - route: PO, short-acting or long-acting depot IM injections, sublingual
  - duration: minimum 6 mo, usually for life

Long-Acting Preparations
- antipsychotics formulated in oil for IM injection
- received on an outpatient basis
- indications: individuals with schizophrenia or other chronic psychosis who relapse because of non-adherence
- dosing: start at low dosages, and then titrate every 2-4 wk to maximize safety and minimize side effects
- should be exposed to oral form prior to first injection
- side effects: risk of EPS, parkinsonism, increased risk of NMS

Table 13. Common Antipsychotic Agents

<table>
<thead>
<tr>
<th></th>
<th>Starting Dose</th>
<th>Maintenance</th>
<th>Maximum</th>
<th>Relative Potency (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typicals</strong> (in order of potency from high to low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine (Trilafon\textsuperscript{a})</td>
<td>8-16 mg PO b/tid</td>
<td>4-8 mg PO t/qid</td>
<td>64 mg/d PO</td>
<td>10</td>
</tr>
<tr>
<td>Loxapine HCl (Loxitane\textsuperscript{a})</td>
<td>10 mg PO bid</td>
<td>12.5-50 mg IM q4-6h</td>
<td>60-100 mg/d PO</td>
<td>25 mg/d PO</td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine\textsuperscript{a})</td>
<td>10-25 mg PO b/t/qid</td>
<td>400 mg/d PO</td>
<td>1000 mg/d PO</td>
<td>100</td>
</tr>
<tr>
<td><strong>Atypicals</strong> (in order of potency from high to low)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone (Risperdal\textsuperscript{a}, Risperdal Consta\textsuperscript{b} for IM long acting preparation, Risperdal M-Tab for melting form – placed on tongue)</td>
<td>1-2 mg OD/bid</td>
<td>4-8 mg/d PO</td>
<td>8 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Paliperidone (Invega\textsuperscript{a})</td>
<td>3 mg/d PO</td>
<td>3-12 mg/d PO</td>
<td>12 mg/d PO</td>
<td>4</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa\textsuperscript{a}, Zyprexa Zydis\textsuperscript{a} for melting form – placed on tongue, Zyprexa Intramuscular\textsuperscript{a})</td>
<td>5 mg/d PO</td>
<td>10-20 mg/d PO</td>
<td>30 mg/d PO</td>
<td>5</td>
</tr>
<tr>
<td>Aripiprazole (Abilify\textsuperscript{a})</td>
<td>10-15 mg/d PO</td>
<td>10-15 mg/d PO</td>
<td>30 mg/d PO</td>
<td>7.5</td>
</tr>
<tr>
<td>Quetiapine (Seroquel\textsuperscript{a}, Seroquel XR\textsuperscript{a} for extended release)</td>
<td>25 mg PO bid</td>
<td>400-800 mg/d PO</td>
<td>800 mg/d PO</td>
<td>75</td>
</tr>
<tr>
<td>Clozapine (Clozaril\textsuperscript{a})</td>
<td>25 mg PO bid</td>
<td>300-600 mg/d PO</td>
<td>600 mg/d PO</td>
<td>100</td>
</tr>
</tbody>
</table>

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia
NEJM 2005;353:1209-23
Study: Randomized, double-blind, active-control trial with median follow-up of 6 mo.
Patients: 1,432 patients with a diagnosis of schizophrenia (as per DSM-IV criteria) and able to take antipsychotic medications (as determined by study doctors). Mean age 41, 74% male, 26% female.
Intervention: 1-4 capsules daily of olanzapine (20.1 mg), quetiapine (543.4 mg), risperidone (3.9 mg), perphenazine (20.8 mg), or ziprasidone (112.8 mg), with dosage at the discretion of the study doctor.
Main Outcome: Discontinuation of treatment for any cause
Results: Olanzapine group had statistically significant lower rate of discontinuation for any cause (64%) from all others (quetiapine – 82%, risperidone – 74%, perphenazine – 75%, ziprasidone – 79%). There were no significant differences in time until discontinuation due to intolerable side effects, however, olanzapine was associated with a significantly higher rate of metabolic side effects.

Typical vs. Atypical Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pros</td>
<td>Inexpensive</td>
<td>Plenty of injectable forms available</td>
</tr>
<tr>
<td>Cons</td>
<td>More EPS</td>
<td>Tardive syndromes in long-term</td>
</tr>
</tbody>
</table>

References

NEJM 2005;353:1209-23
### Table 14. Commonly Used Atypical Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Risperidone (Risperdal&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>Olanzapine (Zyprexa&lt;sup&gt;®&lt;/sup&gt;, Zydis&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>Quetiapine (Seroquel&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>Clozapine (Clozaril&lt;sup&gt;®&lt;/sup&gt;)</th>
<th>Aripiprazole (Abilify&lt;sup&gt;®&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>Lower incidence of EPS than typical antipsychotics at lower doses (&lt;8 mg)</td>
<td>Better overall efficacy compared to haloperidol</td>
<td>Associated with less weight gain compared to clozapine and olanzapine</td>
<td>Most effective for treatment-resistant schizophrenia</td>
<td>Less weight gain and risk of metabolic syndrome compared to olanzapine and a lower incidence of EPS compared to haloperidol</td>
</tr>
<tr>
<td></td>
<td>Associated with less weight gain compared to clozapine and olanzapine</td>
<td>Well tolerated Low incidence of EPS and TD</td>
<td>Compared to clozapine and olanzapine Mood stabilizing</td>
<td>Does not worsen tardive symptoms; may treat them</td>
<td>Approximately 50% of patients benefit, especially paranoid patients and those with onset after 20 yr</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>SE: insomnia, agitation, EPS, H/A, anxiety, prolactin, postural hypotension, constipation, dizziness, weight gain</td>
<td>SE: mild sedation, insomnia, dizziness, minimal anticholinergic, early AST and ALT elevation, restlessness Weight gain associated with increased risk of DM and hyperlipidemia</td>
<td>SE: H/A, sedation, dizziness, constipation Most sedating of first line atypicals</td>
<td>SE: drowsiness/ sedation, hypersalivation, tachycardia, dizziness, EPS, NMS 1% agranulocytosis</td>
<td>SE: H/A, agitation, anxiety, insomnia, weight gain, decreased serum prolactin levels</td>
</tr>
</tbody>
</table>

**Comments**
- Quick dissolve (M-tabs), and long-acting (Consta<sup>®</sup>) formulations available
- Quick dissolve formulation (Zydis<sup>®</sup>) used commonly in ER setting for better compliance IM form available
- Weekly blood counts for at least 1 mo, then q2wk
- Do not use with drugs which may cause bone marrow suppression due to risk of agranulocytosis

Note: Risk of weight gain: Clozapine > Olanzapine > Quetiapine > Risperidone

### Table 15. Side Effects of Antipsychotics

<table>
<thead>
<tr>
<th>System</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anticholinergic</strong></td>
<td>Dry mouth, urinary retention, constipation, blurred vision, toxic-confusional states</td>
</tr>
<tr>
<td><strong>α-Adrenergic Blockade</strong></td>
<td>Orthostatic hypotension, impotence, failure to ejaculate</td>
</tr>
<tr>
<td><strong>Dopaminergic Blockade</strong></td>
<td>Extrapyramidal syndromes, galactorrhea, amenorrhea, impotence, weight gain</td>
</tr>
<tr>
<td><strong>Anti-Histamine</strong></td>
<td>Sedation</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td>Agranulocytosis (clozapine)</td>
</tr>
<tr>
<td><strong>Hypersensitivity Reactions</strong></td>
<td>Liver dysfunction, blood dyscrasias, skin rashes, neuroleptic malignant syndrome, altered temperature regulation (hypothermia or hyperthermia)</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>Metabolic syndrome</td>
</tr>
</tbody>
</table>

### Neuroleptic Malignant Syndrome
- **psychiatric emergency**
- **due to massive dopamine blockade; increased incidence with high potency and depot neuroleptics**
- **risk factors**
  - medication factors: sudden increase in dosage, starting a new drug
  - patient factors: medical illness, dehydration, exhaustion, poor nutrition, external heat load, male, young adults
- **clinical presentation**
  - mental status changes (usually occur first), fever, autonomic reactivity, rigidity
  - develops over 24-72 h
- labs: increased creatine phosphokinase, leukocytosis, myoglobinuria
- **treatment**: discontinue drug, hydration, cooling blankets, dantrolene (hydrantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)
- **mortality**: 5%

### Extrapyramidal Symptoms
- **incidence related to increased dose and potency**
- **acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)**

---

**Anticholinergic Effects**

<table>
<thead>
<tr>
<th>Red as a beet</th>
<th>Hot as a hare</th>
<th>Dry as a bone</th>
<th>Blind as a bat</th>
<th>Mud as a hatter</th>
</tr>
</thead>
</table>

**Metabolic and Cardiovascular Adverse Effects Associated with Antipsychotic Drugs**

*Nat Rev Endocrinol* 2012;8:114-126

Study: Review.

Conclusions: All antipsychotics can cause cardiovascular and metabolic side effects, such as obesity, dyslipidemia, hyperglycemia and metabolic syndrome. Olanzapine and clozapine are most likely to cause these side effects. The mechanism that underlies the metabolic and cardiovascular effects is not fully understood, however, the histamine, dopamine, serotonin, and muscarinic receptors are implicated.
Table 17. Common Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Daily Starting Dose (mg)</th>
<th>Therapeutic Dose (mg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>fluoxetine (Prozac®)</td>
<td>20</td>
<td>20-80</td>
<td>All SSRIs have similar effectiveness but consider side effect profiles and half-lives</td>
</tr>
<tr>
<td></td>
<td>fluvoxamine (Luvox®)</td>
<td>50-100</td>
<td>150-300</td>
<td>Sertraline, citalopram, and escitalopram have the least drug-interactions and are sleep-wake neutral</td>
</tr>
<tr>
<td></td>
<td>paroxetine (Paxil®)</td>
<td>10</td>
<td>20-60</td>
<td>Fluooxetine and paroxetine are the most activating drugs (recommend taking in the AM)</td>
</tr>
<tr>
<td></td>
<td>sertraline (Zoloft®)</td>
<td>50</td>
<td>50-200</td>
<td>Fluoxamine is sedating (should be taken in PM)</td>
</tr>
<tr>
<td></td>
<td>citalopram (Celexa®)</td>
<td>20</td>
<td>20-40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>escitalopram (Lexapro®)</td>
<td>10</td>
<td>10-20</td>
<td></td>
</tr>
</tbody>
</table>

Table 16. Extrapyramidal Symptoms

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Acute or Tardive</th>
<th>Presentation</th>
<th>Onset</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute</td>
<td>Both</td>
<td>Sustained abnormal posture; torsions, twistings, contraction of muscle groups; muscle spasms (e.g. oculogyric crisis, laryngospasm, torticollis)</td>
<td>Acute: within 5 d</td>
<td>Acute: benztropine or diphenhydramine</td>
</tr>
<tr>
<td>Tardive</td>
<td>Elderly females</td>
<td>Motor restlessness; crawling sensation in legs relieved by walking; very distressing, increased risk of suicide and poor adherence</td>
<td>Tardive: &gt;90 d</td>
<td>Acute: lorazepam, propranolol, or diphenhydramine; reduce or change neuroleptic to lower potency</td>
</tr>
<tr>
<td></td>
<td>Elderly females</td>
<td>Tremor; rigidity (cogwheeling); akinesia; postural instability (decreased/absent arm-swing, stooped posture, shuffling gait, difficulty pivoting)</td>
<td>Tardive: &gt;90 d</td>
<td>Acute: benztropine (or diphenhydramine if side effects); reduce or change neuroleptic to lower potency</td>
</tr>
<tr>
<td></td>
<td>Both</td>
<td>Purposeless, constant movements, involving facial and mouth musculature, or less commonly – the limbs</td>
<td>Tardive: &gt;90 d</td>
<td>Tardive: no good treatment; may try clozapine; discontinue drug or reduce dose</td>
</tr>
</tbody>
</table>

Antiparkinsonian Agents (Anticholinergic Agents)
- types
  - benztropine (Cogentin®) 2 mg PO, IM or IV OD (~1-6 mg)
  - amantadine (Symmetrel®) 100 mg PO bid (100-400 mg)
  - diphenhydramine (Benadryl®) 25-50 mg PO/IM qid
- do not always prescribe with neuroleptics
- give antiparkinsonian agents only if at high risk for acute EPS or if acute EPS develops
- do not give for tardive syndromes because they worsen the condition

Antidepressants
- onset of effect
  - relief of neurovegetative symptoms: 1-3 wk
  - relief of emotional/cognitive symptoms: 2-6 wk
- may use mild stimulant (e.g. methylphenidate) for severe neurovegetative symptoms briefly and taper down as antidepressant effect increases
- taper TCAs slowly (over weeks-months) because they can cause withdrawal reactions
- tapering of any kind of antidepressant is usually required and based on the half-life of the medication and the patient's individual sensitivity
- it is important to be particularly vigilant over the first 2 wk of therapy as neurovegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be particularly at risk for suicidal behavior during this time)
- treatment of bipolar disorder
  - monotherapy with antidepressants is not advisable as a switch from depression to mania can occur
  - patients with bipolar disorder should only be treated with an antidepressant if it is combined with a mood stabilizer or antipsychotic
  - for patients taking mood stabilizers or antipsychotics, consider adding or switching to lithium or lamotrigine, or adding an SSRI or buproprion

Table 17. Common Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Daily Starting Dose (mg)</th>
<th>Therapeutic Dose (mg)</th>
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<tr>
<td>SSRI</td>
<td>fluoxetine (Prozac®)</td>
<td>20</td>
<td>20-80</td>
<td>All SSRIs have similar effectiveness but consider side effect profiles and half-lives</td>
</tr>
<tr>
<td></td>
<td>fluvoxamine (Luvox®)</td>
<td>50-100</td>
<td>150-300</td>
<td>Sertraline, citalopram, and escitalopram have the least drug-interactions and are sleep-wake neutral</td>
</tr>
<tr>
<td></td>
<td>paroxetine (Paxil®)</td>
<td>10</td>
<td>20-60</td>
<td>Fluoxamine is sedating (should be taken in PM)</td>
</tr>
<tr>
<td></td>
<td>sertraline (Zoloft®)</td>
<td>50</td>
<td>50-200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>citalopram (Celexa®)</td>
<td>20</td>
<td>20-40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>escitalopram (Lexapro®)</td>
<td>10</td>
<td>10-20</td>
<td></td>
</tr>
</tbody>
</table>
### Table 17. Common Antidepressants (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Daily Starting Dose (mg)</th>
<th>Therapeutic Dose (mg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor®)</td>
<td>37.5-75</td>
<td>75-225</td>
<td>Causes less sexual dysfunction, weight gain, and sedation</td>
</tr>
<tr>
<td></td>
<td>duloxetine (Cymbalta®)</td>
<td>40</td>
<td>40-60</td>
<td></td>
</tr>
<tr>
<td>NDRI</td>
<td>bupropion (Wellbutrin®)</td>
<td>100</td>
<td>300-450</td>
<td>Causes less sexual dysfunction, weight gain, and sedation</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td>Increased risk of seizures at higher doses</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td>Contraindicated with history of seizure, stroke, brain tumor, brain injury, closed head injury</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td></td>
<td></td>
<td>Not recommended for anxiety disorder treatment because of stimulating effects</td>
</tr>
<tr>
<td>TCA (3º Amines)</td>
<td>amitriptyline (Elavil®)</td>
<td>75-100</td>
<td>150-300</td>
<td></td>
</tr>
<tr>
<td></td>
<td>imipramine (Tofranil®)</td>
<td>75-100</td>
<td>150-300</td>
<td></td>
</tr>
<tr>
<td>TCA (2º Amines)</td>
<td>nortriptyline (Aventyl®)</td>
<td>75-100</td>
<td>75-150</td>
<td></td>
</tr>
<tr>
<td></td>
<td>desipramine (Norpramin®)</td>
<td>100-200</td>
<td>150-300</td>
<td></td>
</tr>
<tr>
<td>MAOI</td>
<td>phenelzine (Nardil®)</td>
<td>45</td>
<td>60-90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tranylcypromine (Parnate®)</td>
<td>30</td>
<td>10-60</td>
<td></td>
</tr>
<tr>
<td>NASSA</td>
<td>mirtazapine (Remeron®)</td>
<td>15</td>
<td>15-45</td>
<td>Useful in depression with prominent features of insomnia, agitation, or cachexia</td>
</tr>
</tbody>
</table>

MAOI = monoamine oxidase inhibitors; NASSA = noradrenergic and specific serotonin antagonists; NDRI = norepinephrine and dopamine reuptake inhibitors; RIMA = reversible inhibition of MAO-A; SNRI = serotonin and norepinephrine reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants

### Treatment Strategies for Refractory Depression

- **optimization**: ensuring adequate drug doses for the individual
- **augmentation**: the addition of a medication that is not considered an antidepressant to an antidepressant regimen (e.g. thyroid hormone, lithium, atypical antipsychotics)
- **combination**: the addition of another antidepressant to an existing treatment regimen (e.g. the addition of bupropion to an SSRI or SNRI)
- **substitute**: change in the primary antidepressant (within or outside a class)
- **note**: it is important to fully treat the symptoms of depression in order to decrease rates and severity of relapses
### Table 18. Features of Commonly Used Antidepressant Classes

<table>
<thead>
<tr>
<th>Considerations</th>
<th>TCA</th>
<th>SSRI</th>
<th>MAOI</th>
<th>SNRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCD (clomipramine), melancholic depression</td>
<td>Anxiety states, OCD, eating disorders, seasonal depression, typical and atypical depression</td>
<td>For moderate/severe depression that does not respond to SSRI, atypical depression</td>
<td>Depression, anxiety disorders</td>
<td></td>
</tr>
<tr>
<td>Mode of Action</td>
<td>Block norepinephrine and serotonin reuptake</td>
<td>Block serotonin reuptake only</td>
<td>Irreversible inhibition of monoamine oxidase A and B Leads to ↑ norepinephrine and serotonin</td>
<td>Block norepinephrine and serotonin reuptake</td>
</tr>
<tr>
<td>Side Effects</td>
<td>Anticholinergic effects: (see Table 14) Noradrenergic effects: tremors, tachycardia, sweating, insomnia, erectile and ejaculation problems ↓-↑ adrenergic effects: orthostatic hypotension Antihistamine effects: sedation, weight gain CNS: sedation, stimulation, ↓ seizure threshold CVS: ↑ HR, conduction delay</td>
<td>Fewer than TCA, therefore increased compliance CNS: restlessness, tremor, insomnia, headache, drowsiness GI: N/V, diarrhea, abdominal cramps, weight loss Sexual dysfunction: impotence, anorgasmia CVS: increased HR, conduction delay, serotonin syndrome, EPS, SIADH</td>
<td>Hypertensive crises with tyramine rich foods (e.g. wine, cheese), headache, flushes, palpitations, N/V, photophobia Dizziness, reflex tachycardia, postural hypotension, sedation, insomnia Weight gain Social dysfunction Energizing Minimal anticholinergic and antihistamine effects</td>
<td>Low dose side effects include insomnia (serotonergic) Higher dose side effects include: tremors, tachycardia, sweating, insomnia, dose-dependent increase in diastolic BP (noradrenergic)</td>
</tr>
<tr>
<td>Risk in Overdose</td>
<td>Toxic in OD 3 times therapeutic dose is lethal Presentation: anticholinergic effects, CNS stimulation, then depression and seizures ECG: prolonged QT (duration reflects severity) Treatment: activated charcoal, cathartics, supportive treatment, IV diazepam for seizure, physostigmine salicylate for coma Do not give ipecac, as can cause rapid neurologic deterioration and seizures</td>
<td>Relatively safe in OD</td>
<td>Toxic in OD, but wider margin of safety than TCA</td>
<td>Tachycardia and N/V seen in acute overdose</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>MAOI, SSRI EtOH</td>
<td>SSRIs inhibit P450 enzymes, therefore will affect levels of drugs metabolized by P450 system</td>
<td>EtOH Hypertensive crises with noradrenergic medications (e.g. TCA, decongestants, amphetamines) Serotonin syndrome with serotonergic drugs (e.g. SSRI, tryptophan, dextromethorphan)</td>
<td>MAOI, SSRI Does not seem to inhibit P450 system</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NDRI</th>
<th>RIMA</th>
<th>NASSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Considerations</td>
<td>Depression, seasonal depression</td>
<td>Depression unresponsive to other therapies</td>
</tr>
<tr>
<td>Mode of Action</td>
<td>Block norepinephrine and dopamine reuptake</td>
<td>Reversible inhibitor of monoamine oxidase A Leads to ↑ norepinephrine and serotonin</td>
</tr>
<tr>
<td>Side Effects</td>
<td>CNS: dizziness, headache, tremor, insomnia CVS: dysrhythmia, HTN Gl: dry mouth, N/V, constipation, ↓ appetite Other: agitation, anxiety, anaphylactoid reaction</td>
<td>CNS: dizziness, headache, tremor, insomnia CVS: dysrhythmia, hypotension Gl: dry mouth, N/V, diarrhea, abdominal pain, dyspepsia GU: delayed ejaculation Other: diaphoresis</td>
</tr>
<tr>
<td>Risk in Overdose</td>
<td>Tremors and seizures seen in acute overdose</td>
<td>Risk of fatal overdose when combined with citalopram or clomipramine</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>MAOI</td>
<td>Drugs that reduce seizure threshold: antipsychotics, systemic steroids, quinidine antibiotics, antimalarial drugs</td>
</tr>
</tbody>
</table>
Serotonin Syndrome
- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as SSRI+MAOI, SSRI+tryptophan, MAOI+meperidine, MAOI+tryptophan
- rare but potentially life-threatening adverse reaction to SSRIs, especially when switching from an SSRI to an MAOI
- symptoms include nausea, diarrhea, palpitations, chills, restlessness, confusion, and lethargy but can progress to myoclonus, hyperthermia, rigor and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS (see sidebar, PS38)

Discontinuation Syndrome
- caused by the abrupt cessation of an antidepressant
- observed most frequently with paroxetine, fluvoxamine, and venlafaxine
- symptoms usually begin within 1-3 d and include: anxiety, insomnia, irritability, mood lability, N/V, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy, and myalgia
- treatment: symptoms may last between 1-3 wk, but can be relieved within 24 h by restarting antidepressant therapy at the same dose the patient was taking and initiating a slow taper over several weeks
- consider using a drug with a longer half-life such as fluoxetine

Mood Stabilizers

First-Line
Lithium or Valproic Acid (± antipsychotic)
- before initiating, get baseline: CBC, ECG (if patient >45 yr old or cardiovascular risk), urinalysis, BUN, Cr, electrolytes, TSH
- before initiating lithium: screen for pregnancy, thyroid disease, seizure disorder, neurological, renal, cardiovascular diseases
- may need acute coverage with benzodiazepines or antipsychotics
- use carbamazepine in non-responders and rapid cycling bipolar disorder
- can combine lithium and carbamazepine or valproic acid safely in lithium non-responders
- olanzapine may be used as a mood stabilizer, in conjunction with other mood stabilizers
- lithium and lamotrigine have established antidepressant efficacy

Lithium Toxicity
- clinical diagnosis as toxicity can occur at therapeutic levels
- common causes: overdose, sodium/fluid loss, concurrent medical illness
- clinical presentation
  - GI: severe nausea/vomiting and diarrhea
  - cerebellar: ataxia, slurred speech, lack of coordination
  - cerebral: drowsiness, myoclonus, choreiform or Parkinsonian movements, upper motor neuron signs, seizures, delirium, coma
- management
  - discontinue lithium for several doses and begin again at a lower dose when lithium level has fallen to a non-toxic range
  - serum lithium levels, BUN, electrolytes
  - saline infusion
  - hemodialysis if lithium >2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 h, or deterioration

Second-Line/Adjuvant Mood Stabilizers
Lithium, lamotrigine, divalproex, carbamazepine
Table 19. Commonly Used Mood Stabilizers

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
<th>Lamotrigine (Lamictal®)</th>
<th>Divalproex (Depakote®)</th>
<th>Carbamazepine (Tegretol®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>Maintenance therapy of bipolar disorder</td>
<td>Maintenance treatment of bipolar disorder</td>
<td>Maintenance therapy of bipolar disorder</td>
<td>Maintenance therapy of bipolar disorder</td>
</tr>
<tr>
<td></td>
<td>Treatment of acute mania</td>
<td>Treatment of bipolar depression</td>
<td>Treatment of acute mania</td>
<td>Treatment of acute mania</td>
</tr>
<tr>
<td></td>
<td>Augmentation of antidepressants in MDE and OCD</td>
<td></td>
<td>Rapid cycling bipolar disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schizoaffective disorder</td>
<td></td>
<td>Mixed phase/Dysphoric mania</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic aggression and antisocial behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrent depression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
<td>Unknown</td>
<td>May inhibit 5-HT3 receptors</td>
<td>Depresses synaptic transmission</td>
<td>Depresses synaptic transmission</td>
</tr>
<tr>
<td></td>
<td>Therapeutic response within 7-14 d</td>
<td>May potentiate DA activity</td>
<td>Raises seizure threshold</td>
<td>Raises seizure threshold</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>Adult: 600-1500 mg/d</td>
<td>Starting: 12.5-15 mg/d</td>
<td>750-2500 mg/d</td>
<td>400-1600 mg/d</td>
</tr>
<tr>
<td></td>
<td>Geriatric: 150-600 mg/d</td>
<td>Daily dose: 100-200 mg/d</td>
<td>Usually tid dosing</td>
<td>Usually bid or tid dosing</td>
</tr>
<tr>
<td></td>
<td>Usually daily dosing</td>
<td>Dose adjusted in patients taking other anticonvulsants</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic Level</strong></td>
<td>Adult: 0.8-1.0 mmol/L (1.0-1.25 mmol/L for acute mania)</td>
<td>Therapeutic plasma level not established</td>
<td>17-50 mmol/L</td>
<td>350-700 µmol/L</td>
</tr>
<tr>
<td></td>
<td>Geriatric: 0.5-0.8 mmol/L</td>
<td>Dosing based on therapeutic response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Monitor serum levels until therapeutic (always wait 12 h after dose)</td>
<td>Monitor for suicidality, particularly when initiating treatment</td>
<td>LFTs weekly x 1 mo, then monthly, due to risk of liver dysfunction</td>
<td>Weekly blood counts for first month, due to risk of agranulocytosis</td>
</tr>
<tr>
<td></td>
<td>Then monitor b/w weekly or monthly until a steady state is reached, then q2mo</td>
<td></td>
<td>Watch for signs of liver dysfunction: nausea, edema, malaise</td>
<td>Watch for signs of blood dyscrasias: fever, rash, sore throat, easy bruising</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>GI: N/V, diarrhea, stomach pain</td>
<td>GI: N/V, diarrhea</td>
<td>GI: liver dysfunction, N/V, diarrhea</td>
<td>GI: N/V, diarrhea, hepatic toxicity</td>
</tr>
<tr>
<td></td>
<td>GU: polyuria, polydipsia, GN, renal failure, nephrogenic DI</td>
<td>CNS: ataxia, diziness, diplopia, headache, somnolence</td>
<td>CNS: ataxia, drowsiness, tremor, sedation, cognitive blurring</td>
<td>CNS: ataxia, diziness, slurred speech, drowsiness, confusion, nyctagmus, diplopia</td>
</tr>
<tr>
<td></td>
<td>CNS: fine tremor, lethargy, fatigue, headache</td>
<td>Skin: rash (should discontinue drug because of risk of Stevens-Johnson syndrome), increased lamotrigine levels = increased risk of rash</td>
<td>Other: hair loss, weight gain, transient thrombocytopenia, neural tube defects when used in pregnancy</td>
<td>Hematologic: transient leukopenia (10%), agranulocytosis, aplastic anemia</td>
</tr>
<tr>
<td></td>
<td>Hematologic: reversible leukocytosis</td>
<td>Other: hair loss, weight gain, transient thrombocytopenia, neural tube defects when used in pregnancy</td>
<td></td>
<td>Skin: rash (5% risk; should discontinue drug because of risk of Stevens-Johnson syndrome)</td>
</tr>
<tr>
<td></td>
<td>Other: teratogenic (Erbstein’s anomaly), weight gain, edema, psoriasis, hypothyroidism, hair thinning, muscle weakness, ECG changes</td>
<td>Other: neural tube defects when used in pregnancy</td>
<td></td>
<td>Other: neural tube defects when used in pregnancy</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>NSAIDs decrease clearance</td>
<td>OCP</td>
<td>OCP</td>
<td></td>
</tr>
</tbody>
</table>

### Anxiolytics

- Anxiolytics mask or alleviate symptoms; they do not cure them
- **Indications**
  - Short-term treatment of transient forms of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, organic brain syndrome (agitation in dementia), EPS and akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders
- **Relative Contraindications**
  - Major depression (except as an adjunct to other treatment), history of drug/alcohol abuse, pregnancy, breast feeding
- **Mechanism of Action**
  - Benzodiazepines: potentiate binding of GABA to its receptors; results in decreased neuronal activity
  - Buspirone: partial agonist of 5-HT1A receptors

### Benzodiazepines

- Should be used for limited periods (weeks-months) to avoid dependence
- All benzodiazepines are sedating, be wary in use for the elderly
- Have similar efficacy, so choice depends on half-life, metabolites and route of administration, OD or bid
- Taper slowly over weeks-months because they can cause withdrawal reactions
  - Low dose withdrawal: tachycardia, HTN, panic, insomnia, anxiety, impaired memory and concentration, perceptual disturbances
  - High dose withdrawal: hyperpyrexia, seizures, psychosis, death
- Avoid alcohol because of potentiation of CNS depression; caution with drinking and use of machinery
• side effects
  ▪ CNS: drowsiness, cognitive impairment, reduced motor coordination, memory impairment
  ▪ physical dependence, tolerance

• withdrawal
  ▪ symptoms: anxiety, insomnia, autonomic hyperactivity (less common)
  ▪ onset: 1-2 d (short-acting), 2-4 d (long-acting)
  ▪ duration: weeks-months
  ▪ complications with above 50 mg diazepam/d: seizures, delirium, arrhythmias, psychosis
  ▪ management: taper with long-acting benzodiazepine
  ▪ similar to but less severe than alcohol withdrawal, can be fatal

• overdose
  ▪ commonly used drug in overdose
    ▪ overdose is rarely fatal
  ▪ benzodiazepines are more dangerous and may cause death when combined with alcohol, other CNS depressants or TCAs

Benzodiazepine Antagonist – Flumazenil (Romazicon®)
• use for suspected benzodiazepine overdose
• specific antagonist at the benzodiazepine receptor site

Buspirone (Buspar®)
• primary use: GAD
• may be preferred over benzodiazepines because are non-sedating, no interaction with alcohol, does not alter seizure threshold, not prone to abuse
• onset of action: 2 wk
• side effects: dizziness, drowsiness, nausea, headache, nervousness, EPS

Table 20. Common Anxiolytics

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dose Range (mg/d)</th>
<th>t1/2 (h)</th>
<th>Appropriate Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzodiazepines</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td>clonazepam</td>
<td>0.25-4</td>
<td>18-50</td>
<td>Akathisia, generalized anxiety, seizure prevention, panic disorder</td>
</tr>
<tr>
<td></td>
<td>diazepam</td>
<td>2-40</td>
<td>30-100</td>
<td>Generalized anxiety, seizure prevention, muscle relaxant, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>chlordiazepoxide</td>
<td>5-300</td>
<td>30-100</td>
<td>Sleep, anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>flurazepam</td>
<td>15-30</td>
<td>50-160</td>
<td>Sleep</td>
</tr>
<tr>
<td>Short-acting</td>
<td>alprazolam</td>
<td>0.25-4.0</td>
<td>6-20</td>
<td>Panic disorder, high dependency rate</td>
</tr>
<tr>
<td></td>
<td>lorazepam</td>
<td>0.5-6.0</td>
<td>10-20</td>
<td>Sleep, generalized anxiety, akathisia, alcohol withdrawal, sublingual available for very rapid action</td>
</tr>
<tr>
<td></td>
<td>oxazepam</td>
<td>10-120</td>
<td>8-12</td>
<td>Sleep, generalized anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>temazepam</td>
<td>7.5-30</td>
<td>8-20</td>
<td>Sleep</td>
</tr>
<tr>
<td></td>
<td>triazolam</td>
<td>0.125-0.5</td>
<td>1.5-5</td>
<td>Shortest t1/2, rapid sleep, but rebound insomnia</td>
</tr>
<tr>
<td>Azapirones</td>
<td>buspirone</td>
<td>20-60</td>
<td>2-11</td>
<td>Generalized anxiety</td>
</tr>
<tr>
<td></td>
<td>eszopiclone</td>
<td>2-3</td>
<td>4-6</td>
<td>Sleep</td>
</tr>
</tbody>
</table>

Electroconvulsive Therapy

• induction of a grand mal seizure using an electrical pulse through the brain while the patient is under general anesthesia with a muscle relaxant
• unilateral vs. bilateral electrode placement

• indications
  ▪ depression refractory to adequate pharmacological trial
  ▪ high suicide risk
  ▪ medical risk in addition to depression (dehydration, electrolytes, pregnancy)
  ▪ previous good response to ECT
  ▪ familial response to ECT
  ▪ elderly
  ▪ psychotic depression
  ▪ catatonic features

Geriatric Benzodiazepines
LOT
lorazepam
oxazepam
temazepam
Safe in liver disease because not metabolized by liver

Benzodiazepines used for Alcohol Withdrawal
• Diazepam 20 mg PO/IV q1h prn
• Lorazepam 2-5 mg PO/IV/SI for patients with liver disease, chronic lung disease, or elderly

ECT in Society
Prior to the 1940’s, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by barbaric depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients struggling with mental illness

Efficacy of ECT in Depression: A Meta-Analytic Review
J of ECT 2004; 20:13-20
Study: Meta-analysis of randomized and non-randomized control trials.
Patients: Individuals with unipolar and bipolar depression.
Main Outcomes: The Hamilton Depression Rating scale was used to determine response to treatment.
Results: ECT was found to be superior to simulated ECT, placebo, TCAs, MAOIs, and anti-depressants in general.
Summary: ECT is an efficacious treatment modality, particularly in severe and treatment-resistant depression.
- marked vegetative features
- acute schizophrenia unresponsive to medication
- mania unresponsive to medications

- **side effects:** risk of anesthesia, memory loss (may be retrograde and/or anterograde, tends to resolve by 6 to 9 mo), permanent impairment (controversial), headaches, myalgias
- evidence that unilateral ECT causes less memory loss than bilateral but may not be as effective
- **contraindications:** increased intracranial pressure

References


Koch T. A tour of the psychotropics, 4th ed. Toronto: Mental Health Service, St Michael’s Hospital.


Respirology

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Tina Hu, EBM editor
Dr. Meyer Balter and Dr. Matthew Binnie, staff editors

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<th>Acronym</th>
<th>Definition</th>
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</thead>
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<tr>
<td>AV</td>
<td>arteriovenous</td>
</tr>
<tr>
<td>ASD</td>
<td>atrial septal defect</td>
</tr>
<tr>
<td>AVM</td>
<td>arteriovenous malformation</td>
</tr>
<tr>
<td>ANCA</td>
<td>antineutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>ASA</td>
<td>acetylsalicylic acid (Aspirin®)</td>
</tr>
<tr>
<td>BSA</td>
<td>body surface area</td>
</tr>
<tr>
<td>CBP</td>
<td>congestive heart failure</td>
</tr>
<tr>
<td>CI</td>
<td>cardiac index</td>
</tr>
<tr>
<td>CO</td>
<td>cardiac output</td>
</tr>
<tr>
<td>COP</td>
<td>cryptogenic organizing pneumonia</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CSA</td>
<td>central sleep apnea</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>CPV</td>
<td>central venous pressure</td>
</tr>
<tr>
<td>DIC</td>
<td>disseminated intravascular coagulation</td>
</tr>
<tr>
<td>ECMO</td>
<td>extracorporeal membrane oxygenation</td>
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<td>ERV</td>
<td>expiratory reserve volume</td>
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<tr>
<td>ETT</td>
<td>endotracheal tube</td>
</tr>
<tr>
<td>HPA</td>
<td>human platelet antigen</td>
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<tr>
<td>ICP</td>
<td>inspiratory capacity</td>
</tr>
<tr>
<td>IC</td>
<td>inspired corticosteroid</td>
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<tr>
<td>ILD</td>
<td>interstitial lung disease</td>
</tr>
<tr>
<td>IFF</td>
<td>idiopathic fibrotic lung disease</td>
</tr>
<tr>
<td>ICX</td>
<td>inspiratory capacity</td>
</tr>
<tr>
<td>IPP</td>
<td>inspiratory plateau pressure</td>
</tr>
<tr>
<td>LMA</td>
<td>low molecular weight heparin</td>
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<tr>
<td>LTRA</td>
<td>leukotriene receptor antagonist</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVDP</td>
<td>left ventricular end diastolic pressure</td>
</tr>
<tr>
<td>LVEF</td>
<td>left ventricular ejection fraction</td>
</tr>
<tr>
<td>MAC</td>
<td>Mycobacterium avium complex</td>
</tr>
<tr>
<td>MDI</td>
<td>metered dose inhaler</td>
</tr>
<tr>
<td>MEP</td>
<td>maximum expiratory pressure</td>
</tr>
<tr>
<td>MIP</td>
<td>maximum inspiratory pressure</td>
</tr>
<tr>
<td>MSA</td>
<td>mixed sleep apnea</td>
</tr>
<tr>
<td>MSK</td>
<td>musculoskeletal</td>
</tr>
<tr>
<td>NPPV</td>
<td>non-invasive positive pressure ventilation</td>
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<tr>
<td>PA</td>
<td>arterial partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PAP</td>
<td>arterial partial pressure of oxygen</td>
</tr>
<tr>
<td>PACO2</td>
<td>arterial partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PAPCO2</td>
<td>arterial partial pressure of oxygen</td>
</tr>
<tr>
<td>PACO2</td>
<td>arterial partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PEEP</td>
<td>positive end expiratory pressure</td>
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<td>PFT</td>
<td>pulmonary function tests</td>
</tr>
<tr>
<td>PNS</td>
<td>pulmonary nodules</td>
</tr>
<tr>
<td>PPH</td>
<td>pressure support ventilation</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
</tr>
<tr>
<td>PUD</td>
<td>peptic ulcer disease</td>
</tr>
<tr>
<td>PVC</td>
<td>pulmonary vascular constriction</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
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<tr>
<td>RAP</td>
<td>right atrial pressure</td>
</tr>
<tr>
<td>RBBB</td>
<td>right bundle branch block</td>
</tr>
<tr>
<td>RH</td>
<td>rheumatoid factor</td>
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<tr>
<td>RV</td>
<td>residual volume</td>
</tr>
<tr>
<td>RVEDV</td>
<td>right ventricular end diastolic volume</td>
</tr>
<tr>
<td>RVP</td>
<td>right ventricular systolic pressure</td>
</tr>
<tr>
<td>SCC</td>
<td>squamous cell carcinoma</td>
</tr>
<tr>
<td>SCLC</td>
<td>small cell lung cancer</td>
</tr>
<tr>
<td>SVO2</td>
<td>central venous oxygen saturation</td>
</tr>
<tr>
<td>SIMV</td>
<td>synchronous intermittent mandatory ventilation</td>
</tr>
<tr>
<td>SIRS</td>
<td>systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>SV</td>
<td>stroke volume</td>
</tr>
<tr>
<td>SVC</td>
<td>superior vena cava</td>
</tr>
<tr>
<td>SVRI</td>
<td>systemic vascular resistance index</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
</tr>
<tr>
<td>TUC</td>
<td>total lung capacity</td>
</tr>
<tr>
<td>TNM</td>
<td>tumor, node, metastasis</td>
</tr>
<tr>
<td>TPN</td>
<td>total parenteral nutrition</td>
</tr>
<tr>
<td>UCl</td>
<td>ulcerative colitis</td>
</tr>
<tr>
<td>URTI</td>
<td>upper respiratory tract infection</td>
</tr>
<tr>
<td>V/G</td>
<td>ventilation-to-perfusion</td>
</tr>
<tr>
<td>VATS</td>
<td>video-assisted thoracic surgery</td>
</tr>
<tr>
<td>VC</td>
<td>vital capacity</td>
</tr>
<tr>
<td>VSD</td>
<td>venous septal defect</td>
</tr>
<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
</tr>
<tr>
<td>VT</td>
<td>total volume</td>
</tr>
</tbody>
</table>

## Approach to the Respiratory Patient

### Basic Anatomy Review

![Figure 1. Lung lobes and bronchi](image)

- **Normal**: Normal respiration pattern
- **Obstructive (prolonged expiration)**: *Asthma, COPD*
- **Bradypnea** (slow respiratory rate): *Drug-induced respiratory depression, Diabetic cemia (nonketotic), Increased ICP*
- **Kussmaul’s Breathing** (fast and deep): *Metabolic acidosis, Exercise, Anoxia*
- **Biot’s/Atonic** (irregular with long apneic periods): *Drug-induced respiratory depression, Increased ICP, Brain damage, especially medullary*
- **Cheyne-Stokes Breathing** (changing rates and depths with apneic periods): *Drug-induced respiratory depression, Diabetic cemia (nonketotic), Increased ICP, Brain damage, especially medullary, Apneustic (prolonged inspiratory pause), Pontine lesion*

![Figure 2. Respiration patterns in normal and disease states](image)
### Differential Diagnoses of Common Presentations

#### Table 1. Differential Diagnosis of Dyspnea

**Acute dyspnea (minutes-hours)**
- **Cardiac causes**
  - Ischemic heart disease
  - CHF exacerbation
  - Cardiac tamponade
- **Pulmonary causes**
  - Upper airway obstruction (anaphylaxis, foreign body)
  - Airway disease (asthma, COPD exacerbation, bronchitis)
  - Parenchymal lung disease (ARDS, pneumonia)
  - Pulmonary vascular disease (PE, vasculitis)
  - Pleural disease (pneumothorax, tension pneumothorax)
  - Respiratory control (metabolic acidosis, ASA toxicity)
- **Psychiatric**
  - Anxiety/psychosomatic

**Chronic dyspnea (weeks-months)**
- **Cardiac causes**
  - Valvular heart disease
  - Decreased CO
- **Respiratory causes**
  - Parenchymal lung disease (interstitial disease)
  - Pulmonary vascular disease (pulmonary HTN, vasculitis)
  - Pleural disease (effusion)
  - Airway disease – asthma, COPD
- **Metabolic causes**
  - Severe anemia
  - Hyperthyroidism
- **Neuromuscular and chest wall disorders**
  - Deconditioning, obesity, pregnancy, neuromuscular disease

#### Table 2. Differential Diagnosis of Chest Pain

(see Cardiology and Cardiac Surgery C4 and Emergency Medicine ER21)

<table>
<thead>
<tr>
<th>Nonpleuritic</th>
<th>Pleuritic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary</strong></td>
<td><strong>Pulmonary</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>PE</td>
<td>PE</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Hemothorax</td>
</tr>
<tr>
<td>MI</td>
<td>Neoplasm</td>
</tr>
<tr>
<td>Myocarditis/pericarditis</td>
<td>TB</td>
</tr>
<tr>
<td><strong>Esophageal</strong></td>
<td><strong>Cardiac</strong></td>
</tr>
<tr>
<td>GERD</td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Spasm</td>
<td>Dresser’s syndrome</td>
</tr>
<tr>
<td>Esophagitis</td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td></td>
</tr>
<tr>
<td>Achalasia</td>
<td>GI</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Subphrenic</td>
</tr>
<tr>
<td>Esophageal rupture</td>
<td>Abscess</td>
</tr>
<tr>
<td><strong>Mediastinal</strong></td>
<td><strong>Pleuropericardial</strong></td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Empyema</td>
</tr>
<tr>
<td>Thymoma</td>
<td></td>
</tr>
<tr>
<td><strong>Subdiaphragmatic</strong></td>
<td><strong>GI</strong></td>
</tr>
<tr>
<td>PUD</td>
<td>Costochondritis</td>
</tr>
<tr>
<td>Gastritis</td>
<td>Fractured rib</td>
</tr>
<tr>
<td>Bilary colic</td>
<td>Myositis</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Herpes zoster</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td></td>
</tr>
<tr>
<td>Dissecting aortic aneurysm</td>
<td></td>
</tr>
<tr>
<td><strong>MSK</strong></td>
<td></td>
</tr>
<tr>
<td>Costochondritis</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td></td>
</tr>
<tr>
<td>Ribs</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 3. Differential Diagnosis of Hemoptysis

<table>
<thead>
<tr>
<th>Airway Disease</th>
<th>Parenchymal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute or chronic bronchitis</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>TB</td>
</tr>
<tr>
<td>Bronchogenic CA</td>
<td>Lung abscess</td>
</tr>
<tr>
<td>Bronchial carcinoma tumor</td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disease</strong></td>
<td><strong>Pulmonary:  Lung CA, bronchiectasis, pulmonary fibrosis, abscess, CF, empyema (NOT COPD)</strong></td>
</tr>
<tr>
<td>PE</td>
<td>Endocarditis, A-V fistula</td>
</tr>
<tr>
<td>Elevated pulmonary venous pressure: LVP</td>
<td>Cardiac: Cyanotic heart disease, endocarditis, A-V fistula</td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Other: Other malignancy, primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>Vascular malformation</td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td></td>
</tr>
<tr>
<td>Idiopathic pulmonary hemosiderosis</td>
<td></td>
</tr>
<tr>
<td><strong>Miscellaneous</strong></td>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Impaired coagulation</td>
<td></td>
</tr>
<tr>
<td>Pulmonary endometriosis</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 4. Differential Diagnosis of Cough

<table>
<thead>
<tr>
<th>Airway irritants</th>
<th>Inhaled smoke, dusts, fumes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnasal drip (upper airway cough syndrome)</td>
<td></td>
</tr>
<tr>
<td><strong>Airway Disease</strong></td>
<td><strong>Common Causes of Chronic Cough in the Non-smoking Patient</strong></td>
</tr>
<tr>
<td>URTI including postnasal drip and sinussitis</td>
<td>(cough &gt;3 mo with normal CXR)</td>
</tr>
<tr>
<td>Acute or chronic bronchitis</td>
<td>Gerd</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>Asthma</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Post-nasal drip</td>
</tr>
<tr>
<td>External compression by nose or mass lesion</td>
<td>ACEI</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td></td>
</tr>
<tr>
<td><strong>Parenchymal Disease</strong></td>
<td><strong>Common Causes of Clubbing</strong></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pulmonary: Lung CA, bronchiectasis, pulmonary fibrosis, abscess, CF, empyema (NOT COPD)</td>
</tr>
<tr>
<td>Lung abscess</td>
<td>Cardiac: Cyanotic heart disease, endocarditis, A-V fistula</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>Other: Other malignancy, primary hypertrophic osteoarthropathy</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
</tr>
<tr>
<td><strong>Drug-induced (e.g. ACEI)</strong></td>
<td>Clubbing is not seen in COPD – if present, think malignancy</td>
</tr>
</tbody>
</table>

### Most Common Causes of Hemoptysis
- Most common cause is bronchitis
- 90% of massive hemoptysis is from the bronchial arteries
- Considered “massive” if >600 mL/24 h

### Common Causes of Clubbing
- Pulmonary: Lung CA, bronchiectasis, pulmonary fibrosis, abscess, CF, empyema (NOT COPD)
- Cardiac: Cyanotic heart disease, endocarditis, A-V fistula
- GI: IBD, celiac, cirrhosis
- Endocrine: Graves’
- Other: Other malignancy, primary hypertrophic osteoarthropathy

### Figure 3. Signs of nail clubbing

- Normal
  - IPD > DPD
  - Schamroth’s sign
- Clubbed
  - >180º
  - 160º
  - 160º

Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008. With permission from Elsevier
**Pulmonary Function Tests**

- useful in differentiating the pattern of lung disease (obstructive vs. restrictive)
- assess lung volumes, flow rates, and diffusion capacity (see Figures 5A and 5B)
- note: normal values for FEV₁ are approximately ±20% of the predicted values (for age, sex, and height); ethnicity may affect predicted values

<table>
<thead>
<tr>
<th>Table 5. Comparison of Lung Flow and Volume Parameters in Obstructive vs. Restrictive Lung Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstructive</strong></td>
</tr>
<tr>
<td>• Decreased flow rates (most marked during expiration)</td>
</tr>
<tr>
<td>• Air trapping (increased RV/TLC)</td>
</tr>
<tr>
<td>• Hyperinflation (increased FRC, TLC)</td>
</tr>
<tr>
<td>DDx: Asthma, COPD, CF, bronchiolitis, bronchiectasis*</td>
</tr>
<tr>
<td>FEV₁/FVC                                                                             ↑ or N</td>
</tr>
<tr>
<td>TLC</td>
</tr>
<tr>
<td>RV</td>
</tr>
<tr>
<td>RV/TLC</td>
</tr>
<tr>
<td>DLCO</td>
</tr>
</tbody>
</table>

*Bronchiectasis can be obstructive or mixed

Table 6. Common Respirology Procedures

<table>
<thead>
<tr>
<th>Technique</th>
<th>Purpose</th>
<th>Description</th>
</tr>
</thead>
</table>
| Plethysmography (‘body box’) | Measure FRC | • After a normal expiration the patient inhales against a closed mouthpiece  
• Resultant changes in the volume and pressure of the plethysmograph are used to calculate the volume of gas in the thorax  
• Useful for patients with air trapping |
| He Dilution | Measure FRC | • A known amount of helium is diluted into a patient’s lungs following inspiration  
• Since the amount of helium remains constant, FRC is determined based on the final concentration of the helium in the closed system  
• Only includes airspaces that communicate with the bronchial tree |
| Bronchoscopy | Diagnosis and therapy | • A flexible or rigid bronchoscope is used for visualization of a patient’s airways  
Allows for:  
• Tissue washings for culture and cytology  
• Endobronchial or transbronchial tissue biopsies  
• Removal of secretions/foreign bodies/blood  
• Laser resections  
• Airway stenting  
• Mediastinal lymph nodes can also be sampled using a special bronchoscope equipped with an U/S probe (EBUS) |
**Chest X-Rays**

- see Medical Imaging, MI4

### Table 7. CXR Patterns and Differential Diagnosis

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Signs</th>
<th>Common DDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>Air bronchogram</td>
<td>Acute: water (pulmonary edema), pus (pneumonia), blood (hemorrhage)</td>
</tr>
<tr>
<td>('Airspace disease')</td>
<td>Silhouette sign</td>
<td>Chronic: neoplasm (lymphoma), inflammatory (eosinophilic pneumonia)</td>
</tr>
<tr>
<td></td>
<td>Less visible blood vessels</td>
<td>Chronic infection (TB, fungal)</td>
</tr>
<tr>
<td>Reticular</td>
<td>Increased pulmonary markings</td>
<td>ILD (PF, collagen vascular disease, asbestos, drugs)</td>
</tr>
<tr>
<td>('Interstitial disease')</td>
<td>Honeycombing (RF)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>Cavitary vs. non-cavitary</td>
<td>Cavitary: neoplasm (primary vs. metastatic lung cancer), infectious</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(anaerobic or Gram negative, TB, fungal), inflammatory (RA, Granulomatosis with Polyangiitis [GPA])</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-cavitary: above + sarcoid, Kaposi’s sarcoma (in HIV), silicosis and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>other pneumoconiosis</td>
</tr>
</tbody>
</table>

**Arterial Blood Gases**

- provides information on acid-base and oxygenation status
- see Nephrology, NP14

**Approach to Acid-Base Status**

1. Is the pH acidemic (pH <7.35), alkalemic (pH >7.45), or normal (pH 7.35-7.45)?
2. What is the primary disturbance?
   - metabolic: change in HCO₃⁻ and pH in same direction
   - respiratory: change in HCO₃⁻ and pH in opposite direction
3. Is there appropriate compensation? (see Table 8)
   - metabolic compensation occurs over 2-3 d reflecting altered renal HCO₃⁻ production and excretion
   - respiratory compensation through ventilatory control of P_CO₂ occurs immediately
   - inadequate compensation may indicate a second acid-base disorder
Table 8. Expected Compensation for Specific Acid-Base Disorders

<table>
<thead>
<tr>
<th>Disturbance</th>
<th>$P_{CO_2}$ (mmHg)</th>
<th>$HCO_3^-$ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal ~40</td>
<td>normal ~24</td>
</tr>
<tr>
<td>Respiratory Acidosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↑ 10</td>
<td>↑ 1</td>
</tr>
<tr>
<td>Chronic</td>
<td>↑ 10</td>
<td>↑ 3</td>
</tr>
<tr>
<td>Respiratory Alkalosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↓ 10</td>
<td>↓ 2</td>
</tr>
<tr>
<td>Chronic</td>
<td>↓ 10</td>
<td>↓ 5</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>↓ 1</td>
<td>↓ 1</td>
</tr>
<tr>
<td>Metabolic Alkalosis</td>
<td>↑ 5-7</td>
<td>↑ 10</td>
</tr>
</tbody>
</table>

4. If there is metabolic acidosis, what is the anion gap and osmolar gap?
   - anion gap = $[Na^+] - ([Cl^-] + [HCO_3^-]);$ normal ≤10-15 mEq/L
   - osmolar gap = measured osmolarity – calculated osmolarity = measured – (2$[Na^+] +$ glucose + urea); normal ≤10

5. If anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
   - if not, consider a mixed metabolic picture

Table 9. Differential Diagnosis of Respiratory Acidosis

<table>
<thead>
<tr>
<th>Increased $P_{CO_2}$ secondary to hypoventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Center Depression (Decreased RR)</td>
</tr>
<tr>
<td>Drugs (anesthesia, sedatives, narcotics)</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Increased ICP</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Central apnea</td>
</tr>
<tr>
<td>Supplemental $O_2$ in chronic $CO_2$ retainers (e.g. COPD)</td>
</tr>
<tr>
<td>Neuromuscular Disorders (Decreased Vital Capacity)</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Guillain-Barre syndrome</td>
</tr>
<tr>
<td>Polymyelitis</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>ALS</td>
</tr>
<tr>
<td>Myopathies</td>
</tr>
<tr>
<td>Chest wall disease (obesity, kyphoscoliosis)</td>
</tr>
<tr>
<td>Airway Obstruction (Asthma, COPD)</td>
</tr>
<tr>
<td>Parenchymal Disease</td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>ILD (late stage)</td>
</tr>
<tr>
<td>ADRS</td>
</tr>
</tbody>
</table>

Mechanical Hypoventilation (Inadequate Mechanical Ventilation)

Table 10. Differential Diagnosis of Respiratory Alkalosis

<table>
<thead>
<tr>
<th>Decreased $P_{CO_2}$ secondary to hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoxemia</td>
</tr>
<tr>
<td>Pulmonary disease (pneumonia, edema, PE, interstitial fibrosis)</td>
</tr>
<tr>
<td>Severe anemia</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>High altitude</td>
</tr>
<tr>
<td>CNS disorders</td>
</tr>
<tr>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Gram-negative sepsis</td>
</tr>
<tr>
<td>Drugs (ASA, progesterone, theophylline, catecholamines, psychotropics)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Pain</td>
</tr>
</tbody>
</table>

Mechanical Hyperventilation (Excessive Mechanical Ventilation)

- see Nephrology, NP15 for differential diagnosis of metabolic acidosis and alkalosis
Approach to Hypoxemia

**What is the PaO₂?** (normal 95-100 mmHg)

- PaO₂ < 95 mmHg
  - What is the A-a gradient?
    - (normal < 15 mmHg but increases with age)

  - Increased A-a gradient (>15 mmHg) = lung disease
    - Decreased DL CO
  - Lung normal A-a gradient (<15 mmHg) = normal lungs

  - Pao₂ improves
    - V/Q mismatch
    - Airway disease (asthma, COPD)
    - ILD
    - Alveolar disease
    - Pulmonary vascular disease

  - Pao₂ does not improve
    - Shunt
    - Atelectasis
    - Intralveolar filling (e.g. pulmonary edema, pneumonia)
    - Intracardiac shunt
    - Vascular shunt within lungs

**Figure 9. Pathophysiology of shunt**

**Diseases of Airway Obstruction**

**Pneumonia**

- see Infectious Diseases, ID8

**Asthma**

- see Family Medicine, FM15 and Pediatrics, P91

**Definition**

- chronic inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
- associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli

**Epidemiology**

- common, 7-10% of adults, 10-15% of children
- most children with asthma significantly improve in adolescence
- often family history of atopy (asthma, allergic rhinitis, eczema)
- occupational asthma (organic allergies, isocyanates, animals, etc.)

**Red Flags**

- Severe tachypnea/tachycardia, respiratory muscle fatigue, diminished expiratory effort, cyanosis, silent chest, decreased LOC

- Central cyanosis is not detectable until SaO₂ is <85%. It is more easily detected in polycythemia and less readily detectable in anemia

**Asthma Action Plan**

- Is a written plan developed by patients and their physicians which includes signs and symptoms for patients to recognize their current level of respiratory distress (denoted as ‘green’, ‘yellow’, or ‘red/emergency’ zones) and the personalized treatment options for each zone
### Pathophysiology
- airway obstruction $\rightarrow$ V/Q mismatch $\rightarrow$ hypoxemia $\rightarrow$ ↑ ventilation $\rightarrow$ ↓ $P_{CO_2}$ $\rightarrow$ ↑ pH and muscle fatigue $\rightarrow$ ↓ ventilation, $↑ P_{CO_2}$/↓ pH

### Signs and Symptoms
- dyspnea, wheezing, chest tightness, cough (especially nocturnal), sputum
- symptoms can be paroxysmal or persistent
- signs of respiratory distress (see Figure 4)
- pulsat paradoxic

### Table 11. Criteria for Determining if Asthma is Well Controlled

<table>
<thead>
<tr>
<th>Daytime symptoms &lt;4 d/wk</th>
<th>No asthma-related absence from work/school</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night-time symptoms &lt;1 night/wk</td>
<td>$\beta_2$-agonist use &lt;4 times/wk</td>
</tr>
<tr>
<td>Physical activity normal</td>
<td>FEV$_1$ or PEF &gt;90% of personal best</td>
</tr>
<tr>
<td>Exacerbations mild, infrequent</td>
<td>PEF diurnal variation &lt;10-15%</td>
</tr>
</tbody>
</table>

### Investigations
- $O_2$ saturation
- ABGs (consider in acute exacerbation, along with peak flows, in Emergency Department $\triangleleft$ decreased $P_{O_2}$ during attack (V/Q mismatch) $\triangleleft$ decreased $P_{CO_2}$ in mild asthma (hyperventilation) $\triangleleft$ normal or increased $P_{CO_2}$ is an ominous sign: patient is no longer able to hyperventilate (worsened airway obstruction or respiratory muscle fatigue)
- PFTs (do when stable)

### Table 12. Pulmonary Function Criteria for Diagnosis of Asthma

<table>
<thead>
<tr>
<th>Preferred Measurement</th>
<th>Alternative Measurements</th>
</tr>
</thead>
</table>
| Spirometry showing reversible airway obstruction (1) $↑$ $FEV_1$/FVC below lower limit of normal ($<0.75$ to $0.8$ in adults, $<0.8-0.9$ in children age $6+$) | Peak Expiratory Flow Variability (1) $↑$ in PEF after a bronchodilator or course of controller therapy $\triangleleft$ Adults: PEF $↑$ $60$ L/min (min. $20\%$ OR Diurnal variation $>8\%$ for twice daily readings (20% for multiple daily readings) $\triangleleft$ Children age $6+$: PEF $↑$ $20\%$
| Spirometry showing reversible airway obstruction (2) $↑$ FEV$_1$ $≥$12% (min. 200 mL in adults) after bronchodilator or controller therapy | Positive Challenge Test (1) Methacholine challenge: PC$_{20}$ $<$ 4 mg/mL (4-16 mg/mL is borderline; $>16$ mg/mL is negative) OR (2) Post-exercise: $↓$ FEV$_1$ $≥$10-15% |

### Treatment
- environment: avoid triggers
- patient education: features of the disease, goals of treatment, self-monitoring
- pharmacological
  - symptomatic relief in acute episodes: short-acting $\beta_2$-agonist, anticholinergic bronchodilators, oral steroids, addition of a long acting $\beta_2$-agonist
  - long-term prevention: inhaled/oral corticosteroids, anti-allergic agents, long-acting $\beta_2$-agonists, methylxanthine, LTRA, anti-IgE antibodies (e.g. Xolair$^*$)

### Emergency Management of Asthma
(see Emergency Medicine, ER30)
1. inhaled $\beta_2$-agonist first line (MDI route and spacer device recommended)
2. systemic steroids (PO or IV, if severe)
3. if severe, add anticholinergic therapy $\pm$ magnesium sulphate
4. rapid sequence intubation in life-threatening cases (plus 100% $O_2$, monitors, IV access)
5. SC/IV adrenaline if caused by anaphylaxis, IV salbutamol if unresponsive
6. corticosteroid therapy at discharge

### LTRA in Addition to Usual Care for Acute Asthma in Adults and Children Cochrane DB Syst Rev 2012;CD006100
**Purpose:** To determine if the addition of LTRA is beneficial to patients with acute asthma receiving inhaled bronchodilators and systemic corticosteroids.
**Methods:** RCs in Cochrane Airway Group's Specialised Register of trials that compared LTRA and standard acute asthma vs. placebo and standard in people with acute asthma of any age were included.
**Results:** 8 trials, 1,470 adults and 470 children. For oral treatment, no significant difference between LTRAs and control in hospital admission (RR 0.86; 95% CI 0.60-1.20) but not in children. No significant difference in adverse events between LTRAs and control (RR 0.81; 95% CI 0.62-1.09). Similar results were found for intravenous treatment.
**Conclusions:** Currently, there is no evidence to support routine use ofLTRAs in acute asthma.

### Natural Progression of COPD
- **40s** Chronic productive cough, wheezing occasionally
- **50s** 1st acute chest illness
- **60s** Dyspnea on exertion, increasing sputum, more frequent exacerbations

### Stage
- **Late** Hypoxemia with cyanosis,
- **Stage** polycythemia, hypercapnia (morning headache), cor pulmonale, weight loss

### Asthma Triggers
- URTIs
- Allergens (pet dander, house dust, molds)
- Irritants (cigarette smoke, air pollution)
- Drugs (NSAIDs, $\beta$-blockers)
- Preservatives (sulphites, MSG)
- Other (emotion/anxiety, cold air, exercise, GERD)

### Signs of Poor Asthma Control
- **DANGERS** Daytime Sx $≥$4 times/wk
- Activities reduced
- Nighttime Sx $≥$1 time/wk
- GP visits
- ER visits
- Rescue puffer (SABA) use $≥$4 times/wk
- School and work absences

Consider LABA for night-time symptoms
Chronic Obstructive Pulmonary Disease

- see Family Medicine, FM15

Definition
progressive, and irreversible condition of the lung characterized by chronic obstruction to airflow with many patients having periodic exacerbations, gas trapping, lung hyperinflation, and weight loss

- 2 subtypes (chronic bronchitis or emphysema): usually coexist to variable degrees
- gradual decrease in FEV1 over time with episodes of acute exacerbations

Table 13. Clinical and Pathologic Features of COPD*

<table>
<thead>
<tr>
<th>Chronic Bronchitis</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defined Clinically</td>
<td>Dilution and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis</td>
</tr>
<tr>
<td>Chronic productive cough on most days for at least 3 consecutive months in 2 successive years Obstruction is due to narrowing of the airway lumen by mucosal thickening and excess mucus</td>
<td>Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse, and air trapping</td>
</tr>
<tr>
<td>2 Types</td>
<td>2 Types</td>
</tr>
<tr>
<td>Centriacinar (respiratory bronchioles predominantly affected)</td>
<td>Centreacinar (respiratory bronchioles, alveolar ducts, and alveolar sacs affected)</td>
</tr>
<tr>
<td>Typical form seen in smokers, primarily affects upper lung zones</td>
<td>Accounts for about 1% of emphysema cases</td>
</tr>
<tr>
<td>Panacinar</td>
<td>α1-antitrypsin deficiency, primarily affects lower lobes</td>
</tr>
<tr>
<td>Inherited disorder of defective production of α1-antitrypsin, a protein produced by hepatocytes. Acts in the alveolar tissue by inhibiting the action of proteases from destroying alveolar tissue. When deficient, proteases can destroy lung alveoli resulting in emphysema</td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors
- smoking is #1 risk factor
- others
  - environmental: air pollution, occupational exposure, exposure to wood smoke or other biomass fuel for cooking
  - treatable factors: α1-antitrypsin deficiency, bronchial hyperactivity
  - demographic factors: age, family history, male sex, history of childhood respiratory infections, low socioeconomic status

![Image](409x315 to 434x340)

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Figure 10. Guidelines for asthma management

1HFA Bocethasone or equivalent; *Second-line: LTRA; †Approved for 12 yr and over; *Using a formulation approved for use as a reliever; ‡Approved for 12 yr and over; ¶Using a formulation approved for use as a reliever; #In adults 18 yr and older

Adapted from Can Respir J 2012;19:127-164

**Note that both chronic bronchitis and emphysema can exist without obstruction. Only if obstruction is also present is it termed COPD**

![Image](449x566 to 470x589)

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Pulmonary Embolism in Patients with Unexplained Exacerbation of COPD: Prevalence and Risk Factors

Ann Intern Med 2006;144:390-396
Study: Prospective cohort study of 211 patients with COPD (all current and former smokers) admitted to hospital for severe COPD exacerbation of unknown origin

Measurements: All patients received spiral CT angiogram (CTA) and venous compression ultrasonography of both legs

Results: 25% of patients met diagnostic criteria for PE († CTA or + US)

Conclusions: Prevalence of PE in patients hospitalized for COPD exacerbation of unknown origin is 25%. Therefore, all patients presenting to hospital with COPD exacerbation without obvious cause require PE workup (eg, dopplers or CTA – decision of which to use depends on pre-test probability of the patient)

Non-Invasive Positive Pressure Ventilation for Treatment of Respiratory Failure due to Exacerbations of COPD

Cochrane DB Syst Rev 2009;CD004104
Study: Cochrane Systematic Review. 14 RCTs.
Population: 758 adult patients with COPD and acute respiratory failure due to COPD exacerbation

Intervention: Usual medical care (UMC) and Non-invasive positive ventilation (NPPV) vs. UMC alone

Primary Outcome: Treatment failure, mortality, and tracheal intubation

Results: The risks for all primary outcomes were reduced with NPPV use: treatment failure (RR 0.40); mortality (RR 0.52); and intubation use (RR 0.81). Length of hospital stay was a significant mean 3.24 d shorter, but no difference between ICU length of stay. There is a small and significant improvement in pH (weight mean difference (WMD)=0.04), P AO2 (WMD=0.40 kPa), and respiratory rate (WMD=3.08 bpm) within 1 h post-treatment with NPPV. Complications associated with treatment were reduced in the NPPV treatment arm (RR 0.33).

Conclusion: For patients in respiratory failure due to a COPD exacerbation, NPPV is effective in reducing treatment failure, mortality, and need for intubation when used as a first time treatment adjacent to UMC.

![Image](449x691 to 471x714)

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α1-Antitrypsin Deficiency
Inherited disorder of defective production of α1-antitrypsin, a protein produced by hepatocytes. Acts in the alveolar tissue by inhibiting the action of proteases from destroying alveolar tissue. When deficient, proteases can destroy lung alveoli resulting in emphysema

CO2 Retainers
On ABG, retainers have chronically elevated CO2 levels with a normal pH. Maintain QO2 Sat between RR 92% to prevent Haldane effect and decreased respiratory drive
Signs and Symptoms

Table 14. Clinical Presentation and Investigations for Chronic Bronchitis and Emphysema

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis (Blue Bloater*)</td>
<td>Chronic productive cough</td>
<td>PFT:</td>
</tr>
<tr>
<td></td>
<td>Purulent sputum</td>
<td>↓ FEV₁, ↓ FEV₁/FVC</td>
</tr>
<tr>
<td></td>
<td>Hemoptysis</td>
<td>N TLC, ↓ or N DLCO</td>
</tr>
<tr>
<td></td>
<td>Mild dyspnea initially</td>
<td>CXR:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ AP diameter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ bronchovascular markings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enlarged heart with cor pulmonale</td>
</tr>
<tr>
<td>Emphysema (Pink Puffer*)</td>
<td>Dyspnea (± exertion)</td>
<td>PFT:</td>
</tr>
<tr>
<td></td>
<td>Minimal cough</td>
<td>↓ FEV₁, ↓ FEV₁/FVC</td>
</tr>
<tr>
<td></td>
<td>Tachypnea</td>
<td>↑ TLC (hyperinflation)</td>
</tr>
<tr>
<td></td>
<td>Decreased exercise tolerance</td>
<td>↑ RV (gas trapping)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ DLCO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CXR:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ AP diameter</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flat hemidiaphragm (on lateral CXR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ heart shadow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ retrosternal space</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bulleae</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ peripheral vascular markings</td>
</tr>
</tbody>
</table>

*Note that the distinction between “blue bloaters” and “pink puffers” is more of historical than practical interest as most COPD patients have elements of both.

Table 15. Treatment of Stable COPD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROLONG SURVIVAL</strong></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>Nicotine replacement, bupropion, varenicline</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Prevents cor pulmonale and decreases mortality if used &gt;15/h; indicated if</td>
</tr>
<tr>
<td>Home oxygen</td>
<td>(1) PaO₂ &lt; 55 mmHg or (2) &lt; 60 mmHg with cor pulmonale or polycythemia</td>
</tr>
<tr>
<td><strong>SYMPTOMATIC RELIEF</strong></td>
<td></td>
</tr>
<tr>
<td>Bronchodilators (mainstay of current drug therapy, used in combination)</td>
<td>Short-acting anticholinergics (e.g. ipratropium bromide) and short-acting β₂-agonists (e.g. salbutamol, terbutaline)</td>
</tr>
<tr>
<td></td>
<td>• SABAs: rapid onset but significant side effects at high doses (e.g. hypokalemia)</td>
</tr>
<tr>
<td></td>
<td>• Short-acting anticholinergics more effective than SABAs with fewer side effects but slower onset; take regularly rather than PRN</td>
</tr>
<tr>
<td></td>
<td>LABAs (e.g. salmeterol, formoterol, indacaterol) and long-acting anticholinergics (e.g. tiotropium bromide, glycopyrronium bromide)</td>
</tr>
<tr>
<td></td>
<td>• More sustained effects for moderate to severe COPD</td>
</tr>
<tr>
<td></td>
<td>Inhaled corticosteroid (ICS) + LABA combination (e.g. Advair™: fluticasone + salmeterol, Symbicort™: budesonide + formoterol)</td>
</tr>
<tr>
<td></td>
<td>• ICS/LABA increases effectiveness vs. LABA alone</td>
</tr>
<tr>
<td></td>
<td>Theophylline: weak bronchodilator; limited evidence to suggest combination with bronchodilator</td>
</tr>
<tr>
<td></td>
<td>• Side effects: nervous tremor, nausea/vomiting/diarrhea, tachycardia, arrhythmias, sleep changes</td>
</tr>
<tr>
<td></td>
<td>PDE4 inhibitor: roflumilast (Dairesp®) anti-inflammatory medication useful in COPD with chronic bronchitis, severe airflow obstruction, frequent exacerbations</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>ICS monotherapy is contraindicated and ICS should only be used with a LABA in combination in patients with a history of exacerbations COPD airways are usually inflamed but often not responsive to steroids, therefore avoid chronic systemic glucocorticoids (although oral steroids are very important when treating exacerbations)</td>
</tr>
<tr>
<td>Surgical</td>
<td>Lung volume reduction surgery (resection of emphysematous parts of lung, associated with higher mortality if FEV₁ &lt; 20%), lung transplant</td>
</tr>
<tr>
<td></td>
<td>Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance</td>
</tr>
<tr>
<td>Other</td>
<td>Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance</td>
</tr>
</tbody>
</table>

**Complications of COPD**
- Polycythemia 2° to hypoxemia
- Chronic hypoxemia
- Pulmonary HTN from vasoconstriction
- Cor pulmonale
- Pneumothorax due to rupture of emphysematous bullae

**Influenza Vaccine for Patients with Chronic Obstructive Pulmonary Disease**
Cochrane DB Syst Rev 2006;1:CD002733
Study: Cochrane Systematic Review. 11 RCTs included, 8 specifically in COPD patients.
Population: Six of the studies were done on COPD patients in particular, while the others were on elderly and high-risk individuals. Asthma patients were excluded.
Intervention: Live or inactivated virus vaccines vs. placebo.
Outcome: Exacerbation rates, hospitalizations, mortality, lung function and adverse effects.
Results: In patients with COPD, inactive-vaccine correlated with fewer exacerbations per vaccinated subject than placebo (weighted mean difference (WMD) -0.37, 95% CI -0.84 to -0.11). Inactivated vaccine resulted in fewer influenza-related infections than placebo (WMD 0.19, 95% CI 0.07-0.48). There was also an increased risk of local mild, transient adverse reactions with the vaccine.
Conclusions: There appears to be a reduction in influenza related infections, as well as exacerbations in patients with COPD receiving the vaccine.

**Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease**
Cochrane DB Syst Rev 2009;1:CD001288
Study: Cochrane Systematic Review. 10 RCTs contributed data for analysis.
Population: 1,051 total patients with COPD experiencing acute exacerbations.
Intervention: Oral or parenteral corticosteroids vs. placebo.
Outcome: Rate of treatment failure, length of hospitalization, FEV₁.
Results: Patients receiving corticosteroids experienced fewer treatment failures than placebo (OR 0.50, 95% CI 0.36-0.69). The length of stay in hospital was shorter in patients receiving steroids (1.22 d, 95% CI -2.25 to 0.18). There was also an improvement in FEV₁ at 72 h (140 mL, 95% CI 90-190) and at end of treatment (up to 15 d) (85 mL, 95% CI 10-165). The risk of hypoglycemia was increased (OR 4.95, 95% CI 2.47-9.91).
Conclusions: There appears to be a reduction in rate of treatment failure, reduced length of hospitalization and improved FEV₁ in patients receiving corticosteroid treatment for an acute exacerbation of COPD. However, there is also an increase in significant adverse effects. The ideal length of treatment remains controversial.
Acute Exacerbations of COPD

- **definition**: sustained (>24-48 h) worsening of dyspnea, cough, or sputum production leading to an increased use of medications
- **etiology**: viral URTI, bacteria, air pollution, CHF, PE, MI must be considered
- **management**
  - ABCs, consider assisted ventilation if decreasing LOC or poor ABGs
  - O₂ target 88-92% SaO₂ for CO₂ retainers
  - bronchodilators by MDI with spacer or nebulizer
    - SABA + anticholinergic, e.g. salbutamol and ipratropium bromide via nebulizers x 3 back-to-back q15min
  - systemic corticosteroids: IV solumedrol or oral prednisone
  - antibiotics if purulent sputum
    - simple exacerbation (no risk factors): amoxicillin, 2nd or 3rd generation cephalosporin, macrolide, or TMP/SMX
    - complicated exacerbation (one of: FEV₁ ≤50% predicted, ≥4 exacerbations per year, ischemic heart disease, home O₂ use, chronic oral steroid use): fluoroquinolone or β-lactam + β-lactamase inhibitor (amoxicillin/clavulanate)
  - post exacerbation: rehabilitation with general conditioning to improve exercise tolerance
- **ICU admission**
  - for life threatening exacerbations
  - ventilatory support
    - non-invasive: NPPV, BiPAP
    - conventional mechanical ventilation

Prognosis in COPD

- **prognostic factors**
  - level of dyspnea is the single best predictor
  - development of complications, e.g. hypoxemia or cor pulmonale
  - 5 yr survival
    - FEV₁ <1 L = 50%
    - FEV₁ <0.75 L = 33%
  - **BODE index for risk of death in COPD**
    - greater score = higher probability the patient will die from COPD; score can also be used to predict hospitalization
    - 10 point index consisting of four factors
      - Body mass index (BMI): <21 (+1 point)
      - **Obstruction** (FEV₁): 50-64% (+1), 36-49% (+2), ≤35% (+3)
      - **Dyspnea** (MRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
      - Exercise capacity (6 minute walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)
**Bronchiectasis**

**Definition**
- irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently infected mucus
- usually affects medium sized airways
- *P. aeruginosa* is the most common pathogen; *S. aureus, H. influenzae*, and nontuberculous mycobacteria also common

**Table 16. Etiology and Pathophysiology of Bronchiectasis**

<table>
<thead>
<tr>
<th>Obstruction</th>
<th>Post-infection (results in dilatation of bronchial walls)</th>
<th>Impaired defenses (leads to interference of drainage, chronic infections and inflammation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>Pneumonia</td>
<td>Hypogammaglobulinemia</td>
</tr>
<tr>
<td>Foreign body</td>
<td>TB</td>
<td>CF</td>
</tr>
<tr>
<td>Thick mucus</td>
<td>Measles</td>
<td>Defective leukocyte function</td>
</tr>
<tr>
<td></td>
<td>Pertussis</td>
<td>Ciliary dysfunction (Kartagener’s syndrome: bronchiectasis, sinusitis, situs invs.)</td>
</tr>
<tr>
<td></td>
<td>Allergic bronchopulmonary aspergillosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAC</td>
<td></td>
</tr>
</tbody>
</table>

**Signs and Symptoms**
- chronic cough, purulent sputum (but 10-20% have dry cough), hemoptysis (can be massive), recurrent pneumonia, local crackles (inspiratory and expiratory), wheezes
- clubbing
- may be difficult to differentiate from chronic bronchitis

**Investigations**
- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
  - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
  - specific: "tram tracking" – parallel narrow lines radiating from hilum, cystic spaces, honeycomb like structures
- high-resolution thoracic CT (diagnostic, gold standard)
  - 87-97% sensitivity, 93-100% specificity
  - "signet ring": dilated bronchi with thickened walls where diameter bronchus > diameter of accompanying artery
- sputum cultures (routine + AFB)
- serum Ig levels
- sweat chloride if cystic fibrosis suspected (upper zone predominant)

**Treatment**
- vaccination: influenza and Pneumovax®
- antibiotics (oral, IV, inhaled): routinely used for mild exacerbations, driven by sputum sensitivity; macrolides may be used chronically for an anti-inflammatory effect
- inhaled corticosteroids: decrease inflammation and improve FEV₁
- oral corticosteroids for acute, major exacerbations
- chest physiotherapy, breathing exercises, physical exercise
- pulmonary resection: in selected cases with focal bronchiectasis

**Cystic Fibrosis**

- see Pediatrics, P92

**Pathophysiology**
- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, skin, reproductive organs) and blockage of secretory ducts

**Clinical Features**
- results in severe lung disease, pancreatic insufficiency, diabetes, and azoospermia
- other manifestations: meconium ileus in infancy, distal ileal obstruction in adults, sinusitis, liver disease
- chronic lung infections
  - *S. aureus*: early
  - *P. aeruginosa*: most common
  - *B. cepacia*: worse prognosis but less common
  - *Aspergillus fumigatus*

**Investigations**
- sweat chloride test
  - increased concentrations of NaCl and K⁺ ([Cl⁻] >60 mEq/L is diagnostic in children)
- heterozygotes have normal sweat tests (and no symptoms)
- PFTs
  - early: airflow limitation in small airways
  - late: severe airflow hyperinflation, gas trapping, decreased DLCO (very late)
ABGs
- hypoxemia, hypercapnia later in disease with eventual respiratory failure and cor pulmonale
- CXR
- hyperinflation, increased pulmonary markings (especially upper lobes)

Treatment
- chest physiotherapy and postural drainage
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity), hypertonic saline DNase
- inhaled tobramycin
- antibiotics (e.g. ciprofloxacin)
- lung transplant
- pancreatic enzyme replacements

Prognosis
- depends on: infections (cepacia colonization), FEV₁, acute pulmonary exacerbations, lung transplant vs. non-lung transplant

Interstitial Lung Disease

Definition
- a group of disorders which cause progressive scarring of lung tissue
- this scarring can eventually impair breathing and bloodstream oxygenation

Pathophysiology
- inflammatory and/or fibrosing process in the alveolar walls → distortion and destruction of normal alveoli and microvasculature
- typically associated with
  - lung restriction (decrease in TLC and VC)
  - decreased lung compliance (increased or normal FEV₁/FVC)
  - impaired diffusion (decreased DLCO)
  - hypoxemia due to V/Q mismatch (usually without hypercapnia until end stage)
  - pulmonary HTN and cor pulmonale occur with advanced disease secondary to hypoxemia and blood vessel destruction

Etiology
- >100 known disorders can cause ILD
- majority due to unknown agents or cause

Table 17. Interstitial Lung Diseases

<table>
<thead>
<tr>
<th>UNKNOWN ETIOLOGY</th>
<th>KNOWN ETIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic interstitial pneumonias</td>
<td>ILD Associated with Drugs or Treatments</td>
</tr>
<tr>
<td>UIP (usual interstitial pneumonia e.g. IPF)</td>
<td>Antibiotics (nitrofurantoin)</td>
</tr>
<tr>
<td>NSIP (non-specific interstitial pneumonia)</td>
<td>Anti-inflammatory agents (methotrexate)</td>
</tr>
<tr>
<td>LIP (lymphocytic interstitial pneumonia)</td>
<td>Cardiovascular drugs (amiodarone)</td>
</tr>
<tr>
<td>COP (cryptogenic organizing pneumonia e.g. BOOP)</td>
<td>Antineoplastic agents (chemotherapy agents)</td>
</tr>
<tr>
<td></td>
<td>Ilicit drugs</td>
</tr>
<tr>
<td></td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>ILD Associated with Pulmonary Vasculitis</td>
</tr>
<tr>
<td></td>
<td>Granulomatosis with Polyangitis (GPA)</td>
</tr>
<tr>
<td></td>
<td>Goodpasture’s syndrome</td>
</tr>
<tr>
<td></td>
<td>Idiopathic pulmonary hemosiderosis</td>
</tr>
</tbody>
</table>

In ILD think FASSTEN and BAD RASH
Upper Lung Disease (FASSTEN)
- Farmer’s lung (hypersensitivity pneumonitis)
- Sarcoidosis
- Silicosis
- TB
- Eosinophilic granuloma (Langerhans-cell histiocytosis)
- Neurofibromatosis

Lower Lung Disease (BADRASH)
- Bronchiolitis obliterans with organizing pneumonia (BOOP)
- Asbestosis
- Drugs (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs)
- Rheumatologic disease
- Aspiration
- Scleroderma
- Hamman Rich (acute interstitial pneumonia) and IPF
Signs and Symptoms
• SOB, especially on exertion
• nonproductive cough
• crackles (dry, fine, end-inspiratory)
• clubbing (especially in IPF and asbestosis)
• features of cor pulmonale
• note that signs and symptoms vary with underlying disease process
  e.g. sarcoidosis is seldom associated with crackles and clubbing

Investigations
• CXR/high resolution CT (see Medical Imaging, MI7)
  usually decreased lung volumes
  reticular, nodular, or reticulonodular pattern (nodular <3 mm)
  hilar/mediastinal adenopathy (especially in sarcoidosis)
• PFTs
  restrictive pattern: decreased lung volumes and compliance
  normal or increased FEV1/FVC (>70-80%), e.g. flow rates are often normal or high when
  corrected for absolute lung volume
  DLCO decreased due to V/Q mismatch: less surface area for gas exchange ± pulmonary
  vascular disease
• ABGs
  with progression of disease, hypoxemia and respiratory alkalosis may be present
• other
  bronchoscopy, bronchoalveolar lavage, lung biopsy
  ESR, ANA (lupus), RF (RA), serum-precipitating antibodies to inhaled organic antigens
  (hypersensitivity pneumonitis), c-ANCA (GPA)

Unknown Etiologic Agents

IDIOPATHIC PULMONARY FIBROSIS

Definition
• also known as usual interstitial pneumonia or cryptogenic fibrosing alveolitis
• a progressive, irreversible condition characterized by fibrosis of lung parenchyma with no
  known cause
  chest CT usually shows honeycomb lung, lung biopsy shows UIP (usual interstitial
  pneumonia) pattern
• commonly presents over age 50, incidence rises with age; males > females
• DDx
  other idiopathic interstitial pneumonia, especially NSIP, but also COP and:
  desquamative interstitial pneumonitis (DIP)
  lymphocytic interstitial pneumonitis (LIP): usually 2° to immune conditions such as HIV
  (mostly in children), Sjögren's

Signs and Symptoms
• commonly presents over age 50, incidence rises with age; males > females
• dyspnea on exertion, nonproductive cough, constitutional symptoms, late inspiratory fine
  crackles at lung bases, clubbing

Investigations
• labs (nonspecific, autoimmune serology usually negative)
• CXR: reticular or reticulonodular pattern with lower lung predominance; may appreciate
  honeycombing in advanced disease
• high resolution CT: lower zone peripheral reticular markings, traction bronchiectasis,
  honeycombing, ground glass not prominent in IPF
• biopsy: rarely for UIP as honeycombing makes radiologic diagnosis possible

Treatment
• O2
• N-acetylcysteine (anti-oxidant)
• lung transplantation for advanced disease
• mean survival of 3 to 5 yr after diagnosis

SARCOIDOSIS

Definition
• idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
• characterized pathologically by non-caseating granulomas
• numerous HLA antigens have been shown to play a role and familial sarcoidosis is now recognized
Epidemiology
• typically affects young and middle-aged patients
• higher incidence among African Americans and people at northern latitudes e.g. Scandinavia, Canada

Signs and Symptoms
• asymptomatic, cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
• chest exam often normal
• common extrapulmonary manifestations
  ▪ cardiac (arrhythmias, sudden death)
  ▪ eye involvement (anterior or posterior uveitis)
  ▪ skin involvement (skin papules, erythema nodosum, lupus pernio)
  ▪ peripheral lymphadenopathy
  ▪ arthralgia
  ▪ hepatomegaly ± splenomegaly
• less common extra-pulmonary manifestations involve bone, CNS, and kidney, cardiac (arrhythmias, sudden death)
• two acute sarcoid syndromes
  ▪ Lofgren’s syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
  ▪ Heerfordt-Waldenstrom syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy

Investigations
• CBC (cytopenias from spleen or marrow involvement)
• serum electrolytes, creatinine, liver enzymes, calcium (hypercalcemia/hypercalciuria due to vitamin D activation by granulomas)
• hypergammaglobulinemia, occasionally RF positive
• elevated serum ACE (non-specific and non-sensitive)
• CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
• PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased DLco or mixed obstructive/restrictive
• ECG: to rule out conduction abnormalities
• slit-lamp eye exam: to rule out uveitis

Diagnosis
• biopsy
  ▪ transbronchial lung biopsy, transbronchial lymph node aspiration, endobronchial ultrasound guided surgical (EBUS) biopsy, or mediastinoscopic lymph node biopsy for granulomas
  ▪ in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

Staging
• radiographic, based on CXR
  ▪ Stage 0: normal radiograph
  ▪ Stage I: bilateral hilar lymphadenopathy ± right paratracheal lymphadenopathy
  ▪ Stage II: bilateral hilar lymphadenopathy and diffuse interstitial disease
  ▪ Stage III: interstitial disease only (reticulonodular pattern or nodular pattern)
  ▪ Stage IV: pulmonary fibrosis (honeycombing)

Treatment
• 85% of stage I resolve spontaneously
• 50% of stage II resolve spontaneously
• steroids for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
• methotrexate or other immunosuppressives occasionally used

Prognosis
• approximately 10% mortality secondary to progressive fibrosis of lung parenchyma

Known Etiologic Agents

HYPERSENSITIVITY PNEUMONITIS
• also known as extrinsic allergic alveolitis
• non-IgE mediated inflammation of lung parenchyma (acute, subacute, and chronic forms)
• caused by sensitization to inhaled agents, usually organic dust
• pathology: airway-centered, poorly formed granulomas and lymphocytic inflammation
• exposure usually related to occupation or hobby
  ▪ Farmer’s Lung (Thermophilic actinomycetes)
  ▪ Bird Breeder’s/Bird Fancier’s Lung (immune response to bird IgA)
  ▪ Humidifier Lung (Aureobasidium pullulans)
  ▪ Sauna Taker’s Lung (Aureobasidium spp.)
Signs and Symptoms
- acute presentation: (4-6 h after exposure)
  - dyspnea, cough, fever, chills, malaise (lasting 18-24 h)
  - CXR: diffuse infiltrates
- subacute presentation: more insidious onset than acute presentation
- chronic presentation
  - insidious onset
  - dyspnea, cough, malaise, anorexia, weight loss
  - PFTs: progressively restrictive
  - CXR: predominantly upper lobe reticulonodular pattern
  - type IV (cell mediated, delayed hypersensitivity) reaction (see Rheumatology, R2)
- in both acute and chronic reactions, serum precipitins may be detectable (neither sensitive nor specific)

Treatment
- early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
- systemic corticosteroids can relieve symptoms and speed resolution

PNEUMOCONIOSES
- reaction to inhaled inorganic dusts 0.5-5 µm in size
- no effective treatment, therefore key is exposure prevention through the use of protective equipment
- smoking cessation, annual influenza and pneumococcal vaccination, rehabilitation, lung transplant for endstage disease

Table 18. Pneumoconioses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Etiology</th>
<th>Symptoms</th>
<th>Investigations</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asbestosis</td>
<td>Exposure risks: insulation, shipyard, construction, brake linings, pipe fitters, plumbers</td>
<td>Insidious onset</td>
<td>CXR</td>
<td>Asbestos exposure increases risk of bronchogenic CA and malignant mesothelioma</td>
</tr>
<tr>
<td></td>
<td>Slowly progressive diffuse interstitial fibrosis induced by inhaled asbestos fibers</td>
<td>Cough: paroxysmal, non-productive Fine end-respiratory crackles (increased at bases)Clubbing (much more likely in asbestosis than silicosis or CWP)</td>
<td>Lower &gt; upper lobe Reticulonodular pattern, may develop IPF-like honeycombing Asbestos exposure can also cause pleural and diaphragmatic plaques (+: calcification), pleural effusion, round atelectasis Microscopic examination reveals fungemous bodies: yellow-brown rod-shaped structures which represent asbestos fibers coated in macrophages</td>
<td>Mycobacterial infection (e.g. TB)</td>
</tr>
<tr>
<td>Silicosis</td>
<td>At risk population: sandblasters, rock miners, stone cutters, quarry and highway workers Generally requires &gt; 20 yr exposure; may develop with much shorter but heavier exposure</td>
<td>Dyspnea, cough, and wheezing</td>
<td>CXR</td>
<td>Caplan’s syndrome: rheumatoid arthritis and CWP present as larger nodules</td>
</tr>
<tr>
<td>Coal Worker’s Pneumoconiosis (CWP)</td>
<td>At risk population: coal workers, graphite workers Coal and silica, coal is less fibrogenic than silica</td>
<td>Pathologic hallmark is coal macule Simple CWP No signs or symptoms, usually normal lung function Complicated CWP (also known as progressive massive fibrosis) Dyspnea Course: few patients progress to complicated CWP</td>
<td>Simple CWP CXR: multiple nodular opacities, mostly upper lobe Complicated CWP CXR: opacities larger and coalesce</td>
<td></td>
</tr>
</tbody>
</table>

ILD ASSOCIATED WITH DRUGS OR TREATMENTS

Drug-Induced
- antineoplastic agents: bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate, chlorambucil, BCNU (carmustine)
- antibiotics: nitrofurantoin, penicillin, sulfonamide
- cardiovascular drugs: amiodarone, tocainide
- anti-inflammatory agents: methotrexate, penicillamine
- gold salts
- illicit drugs (heroin, methadone)
- rituximab, anti-TNF-α agents (infliximab, etanercept,adalimumab)

Radiation-Induced
- early pneumonitis: approximately 6 wk post-exposure
- late fibrosis: 6-12 mo post-exposure
- infiltrates conform to the shape of the radiation field
Pulmonary Vascular Disease

Pulmonary Hypertension

Definition
• mean pulmonary arterial pressure >25 mmHg at rest and >30 mmHg with exercise, or a systolic pulmonary artery pressure of >40 mmHg at rest
• in the past, pulmonary HTN was classified as primary or secondary pulmonary HTN, but this classification was modified to a more clinically useful, treatment based classification

Table 19. World Health Organization Classification of Pulmonary HTN

<table>
<thead>
<tr>
<th>Classification</th>
<th>Some Causes</th>
<th>Treatment Options</th>
<th>Consider in All Patients with PH</th>
</tr>
</thead>
</table>
| I. Pulmonary Arterial HTN | Idiopathic  
Collagen vascular disease (scleroderma, SLE, RA)  
Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome)  
Portopulmonary HTN  
HIV infection  
Drugs and toxins (e.g. anorexigens)  
Pulmonary veno-occlusive disease  
Schistosomiasis  
Pulmonary capillary hemangiomatosis  
Sickle cell disease | No effective treatment  
CCBs or advanced therapy often needed  
The latter includes: prostanoids, endothelin receptor antagonists, PDE5 inhibitors  
Lung transplantation | Oxygen therapy  
Exercise  
Consider anticoagulation |
| II. Pulmonary HTN due to Left Heart Disease | Left-sided atrial or ventricular heart disease (e.g. LV dysfunction)  
Left-sided valvar heart disease (e.g. aortic stenosis, mitral stenosis) | Treat underlying heart disease | |
| III. Pulmonary HTN due to Lung Disease and/or Hypoxia | Parenchymal lung disease (COPD, interstitial fibrosis, cystic fibrosis)  
Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep disordered breathing) | Treat underlying cause of hypoxia and correct with supplemental oxygen (proven mortality benefit) | |
| IV. Chronic Thromboembolic Pulmonary HTN (CTEPH) | Thromboembolic obstruction of proximal pulmonary arteries  
Obstruction of distal pulmonary arteries – PE (thrombus, foreign material, tumor, in situ thrombosis) | Anticoagulation, thromboendarterectomy | |
| V. Pulmonary HTN with Unclear Multifactorial Mechanisms | Hematologic disorders  
Systemic disorders (e.g. sarcoidosis)  
Metabolic disorders  
Extrinsic compression of central pulmonary veins (tumor, adenopathy, fibrosing mediastinitis) | Treat underlying cause | |


Mechanisms of Pulmonary HTN (Simplified)
- hypoxic vasoconstriction
  ▪ chronic hypoxia causes pulmonary vasoconstriction by a variety of actions on the pulmonary artery endothelium and smooth muscle cells, such as: down regulation of endothelial nitric oxide synthase and alteration of voltage gated potassium channels leading to vasoconstriction
  ▪ causes: COPD, chronic alveolar hypoxia
- decreased area of pulmonary vascular bed
  ▪ leads to a rise in resting pulmonary arterial pressure
  ▪ causes: collagen vascular disease, HIV infection, drugs and toxins, thrombotic or embolic disease, inflammatory, pulmonary capillary hemangiomatosis, interstitial fibrosis, CF
- volume and pressure overload
  ▪ significant HTN only occurs with excessive volume overload, since pulmonary artery pressure will not rise in otherwise normal lung until pulmonary blood flow exceeds 2.5x the basal rate
  ▪ causes: congenital systemic to pulmonary shunts (e.g. VSD, ASD, PDA), portopulmonary HTN, left-sided heart conditions, pulmonary veno-occlusive disease, extrinsic compression of central pulmonary veins

Pulmonary arterial pressures are measured by pulmonary artery catheters (i.e. Swan-Ganz catheter) which are inserted into a large vein (often internal jugular). A balloon at the end of the catheter tip is inflated causing the catheter to advance through the right side of the heart and into the pulmonary artery. This allows for the measurement of RA, RV, PA, and pulmonary capillary wedge pressures as well as sampling of mixed venous blood. A thermodiluter near the end of the catheter also allows for assessment of cardiac output by thermodilution.
IDIOPATHIC PULMONARY ARTERIAL HTN (i.e. PRIMARY PULMONARY HTN)

Definition
- pulmonary HTN in the absence of a demonstrable cause
- exclude
  - left-sided cardiac valvular disease
  - myocardial disease
  - congenital heart disease
  - any clinically significant parenchymal lung disease
  - systemic connective-tissue disease
  - chronic thromboembolic disease

Epidemiology
- usually presents in young women (20-40 yr); mean age of diagnosis is 36 yr
- most cases are sporadic; familial predisposition in 10% of cases, some linked to mutations in BMPR2
- may be associated with the use of anorexic drugs (e.g. Aminorex®, Fenfluramine®), amphetamines and cocaine

Signs and Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Loud, palpable P₂</td>
</tr>
<tr>
<td>Fatigue</td>
<td>RV heave</td>
</tr>
<tr>
<td>Subternal chest pain</td>
<td>Right-sided S₃ (due to RVH)</td>
</tr>
<tr>
<td>Syncope</td>
<td>Systolic murmur (tricuspid regurgitation (TR))</td>
</tr>
<tr>
<td>Symptoms of underlying disease</td>
<td>If RV failure: right sided S₃, increased JVP, positive HJR, peripheral edema, TR Reynaud’s phenomenon</td>
</tr>
</tbody>
</table>

Investigations
- CXR: enlarged central pulmonary arteries, cardiac changes due to RV enlargement (filling of retrosternal air space)
- ECG
  - RVH/right-sided strain (see Cardiology and Cardiac Surgery, C7)
- 2-D echo doppler assessment of right ventricular systolic pressure
- cardiac catheterization: direct measurement of pulmonary artery pressures (necessary to confirm diagnosis)
- PFTs to assess for underlying lung disease: DLCO usually reduced; volumes and flows normal
- CT angiogram to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary HTN; other serologic markers can be used in the appropriate clinical setting

Prognosis
- 2-3 yr mean survival from time of diagnosis
- survival decreases to approximately 1 yr if severe pulmonary HTN or right-heart failure

Pulmonary Embolism

Definition
- lodging of a blood clot in the pulmonary arterial tree with subsequent increase in pulmonary vascular resistance, impaired V/Q matching, and possibly reduced pulmonary blood flow

Etiology and Pathophysiology
- one of the most common causes of preventable death in the hospital
- proximal leg thrombi (popliteal, femoral, or iliac veins) are the source of most clinically recognized pulmonary emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE
- fewer than 30% of patients have clinical evidence of DVT (e.g. leg swelling, pain, or tenderness)
- always suspect PE if patient develops fever, sudden dyspnea, chest pain, or collapse 1-2 wk after surgery

Guidelines for Vasodilator Response in Pulmonary Arterial HTN
- Patients with IPAH that respond to vasodilators acutely, have an improved survival with long-term use of CCBs
- Vasoreactivity testing: short-acting agent such as IV epoprostenol, IV adenosine, or inhaled NO
- Positive vasodilator response: mean PAP fall of at least 10 mmHg to ≤40 mmHg with an increased or unchanged cardiac output (European Society of Cardiology)
- Positive vasodilator response: should be considered as candidate for trials of oral CCB therapy

Medical Therapy for Pulmonary Arterial HTN
- ACCP Evidence-Based Clinical Practice Guidelines. Chest 2012;141(Suppl.6):126

Vicwhow’s Triad
- Venous stasis
- Endothelial cell damage
- Hypercoagulable states

Multidetector Computed Tomography for Acute Pulmonary Embolism (PIOPED II Trial)
- Study: Multicenter, prospective study investigating accuracy of computed tomography angiography (CTA) alone and combined with venous phase imaging (CTA-CTV) for the diagnosis of PE
- Patients: 824 patients of several thousand eligible for study received reference diagnosis of PE (including a Wells score) prior to imaging
- Outcomes: Diagnosis of pulmonary embolism
- Results: 777 of 824 patients had adequate CTA for interpretation. PE was diagnosed in 192 of the 824 patients. Sensitivity was 83% (150 of 181 patients, 95% CI 0.76-0.92) and specificity was 98% (567 of 592 patients, 95% CI 0.93-0.97).
- Conclusion: CTA is effective for diagnosing or excluding PE in accordance with assessment of clinical pre-test probability. When clinical probability is inconsistent with imaging results, further investigations are required to rule out PE.
Risk Factors
- stasis
  - immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
  - obesity, CHF
  - chronic venous insufficiency
  - endothelial cell damage
  - post-operative injury, trauma
- hypercoagulable states
  - underlying malignancy (particularly adenocarcinoma)
  - cancer treatment (chemotherapy, hormonal)
  - exogenous estrogen administration (OCP, HRT)
  - pregnancy, post-partum
  - prior history of DVT/PE, family history
  - nephrotic syndrome
  - coagulopathies: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease
- increasing age

Investigations (if highly suspicious, go straight to CT angiogram)
- see Emergency Medicine, Figure 13, ER34

Table 21. Common Investigations for Pulmonary Embolism

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Purpose/Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Angiogram</td>
<td>Filling defect indicative of embolus; negative angiogram excludes clinically relevant PE</td>
</tr>
<tr>
<td>(Gold Standard)</td>
<td>More invasive, and harder to perform than CT, therefore done infrequently</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Highly sensitive D-dimer result can exclude DVT/PE if pretest probability is already low</td>
</tr>
<tr>
<td>CT Angiogram</td>
<td>Diagnosis and management uncertain for small filling defects</td>
</tr>
<tr>
<td></td>
<td>CT may identify an alternative diagnosis if PE is not present</td>
</tr>
<tr>
<td></td>
<td>CT scanning of the proximal leg and pelvic veins can be done at the same time and may be helpful</td>
</tr>
<tr>
<td>Venous Duplex U/S or Doppler</td>
<td>With leg symptoms</td>
</tr>
<tr>
<td></td>
<td>Positive test rules in proximal DVT</td>
</tr>
<tr>
<td></td>
<td>Negative test rules out proximal DVT</td>
</tr>
<tr>
<td></td>
<td>Without leg symptoms</td>
</tr>
<tr>
<td></td>
<td>Positive test rules in proximal DVT</td>
</tr>
<tr>
<td></td>
<td>Negative test does not rule out a DVT: patient may have non-occlusive or calf DVT</td>
</tr>
<tr>
<td>ECG</td>
<td>Findings not sensitive or specific</td>
</tr>
<tr>
<td></td>
<td>Sinus tachycardia most common; may see non-specific ST segment and T wave changes</td>
</tr>
<tr>
<td></td>
<td>RV strain, RAD, RBBB, S1-Q3-T3 with massive embolization</td>
</tr>
<tr>
<td>CXR</td>
<td>Frequently normal; no specific features</td>
</tr>
<tr>
<td></td>
<td>Atelectasis (subsegmental), elevation of a hemidiaphragm</td>
</tr>
<tr>
<td></td>
<td>Pleural effusion: usually small</td>
</tr>
<tr>
<td></td>
<td>Hampton’s hump: cone-shaped area of peripheral opacification representing infarction</td>
</tr>
<tr>
<td></td>
<td>Westermark’s sign: dilated proximal pulmonary artery with distal oligemia/decreased vascular markings</td>
</tr>
<tr>
<td></td>
<td>(difficult to assess without prior films)</td>
</tr>
<tr>
<td></td>
<td>Dilatation of proximal PA: rare</td>
</tr>
<tr>
<td>V/Q Scan</td>
<td>Very sensitive but low specificity</td>
</tr>
<tr>
<td></td>
<td>Order scan if</td>
</tr>
<tr>
<td></td>
<td>CXR normal, no COPD</td>
</tr>
<tr>
<td></td>
<td>Contraindication to CT (contrast allergy, renal dysfunction, pregnancy)</td>
</tr>
<tr>
<td></td>
<td>Avoid V/Q scan if</td>
</tr>
<tr>
<td></td>
<td>CXR abnormal or COPD</td>
</tr>
<tr>
<td></td>
<td>Inpatient</td>
</tr>
<tr>
<td></td>
<td>Suspect massive PE</td>
</tr>
<tr>
<td></td>
<td>Results</td>
</tr>
<tr>
<td></td>
<td>Normal: excludes the diagnosis of PE</td>
</tr>
<tr>
<td></td>
<td>High probability: most likely means PE present, unless pre-test probability is low</td>
</tr>
<tr>
<td></td>
<td>60% of V/Q scans are nondiagnostic</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Useful to assess massive or chronic PE</td>
</tr>
<tr>
<td></td>
<td>Not routinely done</td>
</tr>
<tr>
<td>ABG</td>
<td>No diagnostic use in PE (insensitive and nonspecific)</td>
</tr>
<tr>
<td></td>
<td>May show respiratory alkalosis (due to hyperventilation)</td>
</tr>
</tbody>
</table>

Clinical Prediction Rule for Pulmonary Embolism

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs of DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>No more likely alternative diagnosis (using H&amp;P, CXR, ECG)</td>
<td>3.0</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous 4 wk</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous PE/DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>HR &gt; 100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Clinical Probability
- Low (0-2): 3%
- Intermediate (3-6): 28%
- High (>6): 78%

Modified Wells: >4 PE likely; ≤4 PE unlikely

PE Rule Out Criteria (PERC)
Prospective Multicenter Evaluation of the Pulmonary Embolism Rule Out Criteria

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Rule Out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;50 yr</td>
<td></td>
</tr>
<tr>
<td>Heart rate less than 100 bpm</td>
<td></td>
</tr>
<tr>
<td>Oxygenhemoglobin saturation &gt;95%</td>
<td></td>
</tr>
<tr>
<td>No hemoptysis</td>
<td></td>
</tr>
<tr>
<td>No estrogen use</td>
<td></td>
</tr>
<tr>
<td>No prior DVT or PE</td>
<td></td>
</tr>
<tr>
<td>No unilateral leg swelling</td>
<td></td>
</tr>
<tr>
<td>No surgery or trauma requiring hospitalization within the past 4 wk</td>
<td></td>
</tr>
</tbody>
</table>

Acute PE can probably be excluded without further diagnostic testing if the patient meets all PERC criteria AND there is a low clinical suspicion for PE, according to either the Wells criteria or a low gestalt probability determined by the clinician prior to diagnostic testing for PE.

Evaluation of a Suspected Pulmonary Embolism

<table>
<thead>
<tr>
<th>Low clinical probability of embolism</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>D-dimer (+ve)</td>
<td>CT scan (+ve) → ruled in (–ve) ruled out (–ve) ruled out</td>
</tr>
<tr>
<td>Intermediate or high probability</td>
<td>CT scan (–ve) → ruled out (–ve) ruled in</td>
</tr>
</tbody>
</table>

Notes
- Use D-dimers only if low clinical probability, otherwise, go straight to CT.
- If using V/Q scan (CT contrast allergy or renal failure):  
  - Negative V/Q scan rules out the diagnosis
  - High probability V/Q scan can only rules in the diagnosis if have high clinical suspicion
  - Inconclusive V/Q scan requires leg U/S to look for DVT or CT.

Classic ECG finding of PE is S1-Q3-T3 (inverted T3), but most commonly see only sinus tachycardia

D-dimer is elevated in patients with recent surgery, cancer, inflammation, infection, and severe renal dysfunction. It has good sensitivity and negative predictive value, but poor specificity and positive predictive value.
Treatment
- admit for observation (patients with DVT only are often sent home on LMWH)
- oxygen: supplemental O₂ if hypoxic or short of breath
- pain relief: analgesics if chest pain – narcotics or acetaminophen
- acute anticoagulation: therapeutic-dose SC LMWH or IV heparin – start ASAP
  - anticoagulation stops clot propagation, prevents new clots and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months
  - get baseline CBC, INR, aPTT ± renal function ± liver function
  - for SC LMWH: dalteparin 200 U/kg once daily or enoxaparin 1 mg/kg bid – no lab monitoring – avoid or reduce dose in renal dysfunction
- for IV heparin: bolus of 75 U/kg (usually 5,000 U) followed by infusion starting at 20 U/kg/h – aim for aPTT 2-3x control
- long-term anticoagulation
  - warfarin: start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 d and until INR in target range of 2-3 for at least 2 d
  - LMWH instead of warfarin for pregnancy, active cancer, or high bleeding risk patients
  - dabigatran has been shown to have lower bleeding risk than warfarin
- IV thrombolytic therapy
  - if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
  - hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding
- interventional thrombolytic therapy
  - massive PE is preferentially treated with catheter-directed thrombolysis by an interventional radiologist
  - works better than IV thrombolytic therapy and fewer contraindications
- IVC filter: only if recent proximal DVT + absolute contraindication to anticoagulation
- duration of long-term anticoagulation: individualized, however generally:
  - if reversible cause for PE (surgery, injury, pregnancy, etc.): 3-6 mo
  - if PE unprovoked: 6 mo to indefinite
  - if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite

Thromboprophylaxis
- mandatory for most hospital patients: reduces DVT, PE, all-cause mortality, cost-effective
- start ASAP
- continue at least until discharge or recommend extending for 35 d post-operatively, if major orthopedic surgery

Table 22. VTE Risk Categories and Prophylaxis (see Hematology, H35)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Prophylaxis Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Thrombosis Risk</td>
<td>No specific prophylaxis</td>
</tr>
<tr>
<td>Medical patients: fully mobile</td>
<td>Frequent ambulation</td>
</tr>
<tr>
<td>Surgery: &lt;30 min, fully mobile</td>
<td></td>
</tr>
<tr>
<td>Moderate Thrombosis Risk</td>
<td>LMWH</td>
</tr>
<tr>
<td>Most general, gynecologic, urologic surgery</td>
<td>Low dose unfractionated heparin</td>
</tr>
<tr>
<td>Sick medical patients</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>High Thrombosis Risk</td>
<td>LMWH</td>
</tr>
<tr>
<td>Arthritis, hip fracture surgery</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>Major trauma, spinal cord injury</td>
<td>Warfarin (INR 2-3)</td>
</tr>
<tr>
<td></td>
<td>Dabigatran</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td></td>
<td>Low dose unfractionated heparin</td>
</tr>
<tr>
<td>High Bleeding Risk</td>
<td>TED stockings, pneumatic compression devices</td>
</tr>
<tr>
<td>Neurosurgery, intracranial bleed</td>
<td>LMWH or low dose heparin when bleeding risk decreases</td>
</tr>
<tr>
<td>Active bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism
NEJM 2013;368:709-719
Study: Two double-blind, RCTs; one comparing against placebo, the other against active treatment.
Population: 4,199 patients (2,856 in active-control study, 1,343 in placebo-control study) with VTE who had completed at least 3 mo of therapy.
Intervention: In the active-control study, patients randomized to either 150 mg dabigatran or warfarin (INR 2.0-3.0). Patients in the placebo-control study received either 150 mg dabigatran or placebo.
Outcome: Recurrence of VTE, risk of major or clinically relevant bleed.
Results: In the active-control study, there was a hazard ratio (HR) of 1.44 (95% CI 0.79-2.64) for non-inferiority of recurrent VTE with dabigatran vs. warfarin. HR of major or clinically relevant bleed was 0.94 (95% CI 0.41-0.71). In the placebo-control study, the HR of VTE with dabigatran vs. placebo was 0.98 (95% CI 0.02-0.95). HR of major or clinically relevant bleed was 2.92 (95% CI 1.52-5.60).
Conclusions: Dabigatran appears to be non-inferior to warfarin in the prevention of VTE recurrence. Dabigatran is associated with a lower risk of major or clinically relevant bleed than warfarin, but greater than placebo.

Excluding Pulmonary Embolism at Bedside without Diagnostic Imaging
Study: Multicenter, prospective cohort study.
Patients: 930 patients with suspected PE at emergency departments of 4 tertiary care hospitals in Canada.
Intervention: A Wells score was used to determine patient’s pretest probability (PTP) of PE along with D-dimer test.
Main Outcomes: Diagnosis of PE and the development of thromboembolic events at 3 mo follow-up.
Results: One of 759 patients in whom PE was initially ruled out developed a thromboembolic event during follow-up (0.1% CI 0.0%-0.0%). One of the 437 patients with negative D-dimers and low clinical PTP developed PE during follow up (MPV 99.5%, CI 98.1-100%).
Conclusion: Managing patients with suspected pulmonary embolism on the basis of PTP and D-dimer results is safe and decreases the need for diagnostic imaging.

Workup for Idiopathic VTE
Thrombophilia Workup: recurrent or idiopathic DVT/PE, age <50, FHx, unusual location, massive
Malignancy Workup: 12% of patients with idiopathic VTE will have a malignancy
Pulmonary Vasculitis

Table 23. Pulmonary Vasculitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Definition</th>
<th>Pulmonary Features</th>
<th>Extra-Pulmonary Features</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with Polyangiitis (Wegener’s Granulomatosis) (see Nephrology, NP24)</td>
<td>Systemic vasculitis of medium and small arteries</td>
<td>Necrotizing granulomatous lesions of the upper and lower respiratory tract</td>
<td>Focal necrotizing lesions of arteries and veins; crescentic glomerulonephritis</td>
<td>CXR: nodules, cavities, and alveolar opacities c-ANCA Tissue confirmation</td>
<td>Corticosteroids and cyclophosphamide or rituximab</td>
</tr>
<tr>
<td>Churg-Strauss Syndrome (Granulomatosis with Polyangiitis)</td>
<td>Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia</td>
<td>Asthma Infiltrates</td>
<td>Life-threatening systemic vasculitis involving the lungs, pericardium and heart, kidneys, skin, and PNS (mononeuritis multiplex)</td>
<td>Peripheral eosinophilia is the most common finding p-ANCA may be positive Biopsy involved tissue</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Goodpasture’s Disease (see Nephrology, NP24)</td>
<td>A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung</td>
<td>Hemoptysis May follow an influenza infection</td>
<td>Anemia</td>
<td>CXR: may see alveolar infiltrates if hemorrhage is profuse ELISA test with anti-GBM antibodies Renal biopsy/indirect immunofluorescence shows linear staining</td>
<td>Acutely: corticosteroids, plasmapheresis Immunosuppressive therapy Severe cases: bilateral nephrectomy</td>
</tr>
</tbody>
</table>

Systemic Lupus Erythematosus, Rheumatoid Arthritis, Scleroderma

See Rheumatology, RH8

Pulmonary Edema

- see Cardiology and Cardiac Surgery, C35

Diseases of the Mediastinum and Pleura

Mediastinal Masses

Definition
- mediastinum: bound by the thoracic inlet, diaphragm, sternum, vertebral bodies, and the pleura
- can be broken down into 3 compartments: anterior, middle, and posterior

Etiology and Pathophysiology
- diagnosis is made by location and patient’s age
- anterior compartment: more likely to be malignant
  - “Four Ts” (see sidebar), lymphoma, lipoma, pericardial cyst
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumor, lymphoma, lymph node enlargement, aortic aneurysm
- posterior compartment
  - neurogenic tumors, meningocoele, enteric cysts, lymphoma, diaphragmatic hernias, esophageal tumor, aortic aneurysm

Signs and Symptoms
- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner’s syndrome, facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes (e.g. myasthenia gravis [thymomas])

Investigations
- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumors
- U/S (best for assessment of structures in close proximity to the heart and pericardium)
- radionuclide scanning: 131I (for thyroid), gallium (for lymphoma)
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP, β-hCG
- biopsy (mediastinoscopy, percutaneous needle aspiration)
Management
- excision if symptomatic enlarging benign masses or concerns of malignancy
- resect bronchogenic cysts and localized neurogenic tumors via minimally invasive video assisted procedures
- exploration via sternotomy or thoracotomy
- diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumor, or unresectable invasive malignancy
- ± post-operative radiotherapy/chemotherapy if malignant

Mediastinitis
- commonest causes: post-operative complications of cardiovascular or thoracic surgical procedures

Acute
- etiology
  - complication of endoscopy (e.g. esophageal perforation providing entry point for infection)
  - esophageal or cardiac surgery
  - tumor necrosis
- signs and symptoms
  - fever, substernal pain
  - pneumomediastinum, mediastinal compression
  - Hamman's sign (auscultatory “crunch” during cardiac systole)
- treatment
  - antibiotics, drainage, ± surgical closure of perforation

Chronic
- usually granulomatous process or fibrosis related to previous infection (e.g. histoplasmosis, TB, sarcoidosis, syphilis)

Pleural Effusions
Definition
- excess amount of fluid in the pleural space

Etiology
- disruption of normal equilibrium between pleural fluid formation/entry and pleural fluid absorption/exit
- pleural effusions are classified as transudative or exudative
  - distinguish clinically using Light’s Criteria, which has a sensitivity of 98% and specificity of 83% for identifying exudative pleural effusions

Table 24. Laboratory Values in Transudative and Exudative Pleural Effusion

<table>
<thead>
<tr>
<th></th>
<th>Light’s Criteria</th>
<th>Modified Light’s Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein – pleural/serum</td>
<td>&gt;0.5</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>LDH – pleural/serum</td>
<td>&gt;0.6</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Pleural LDH</td>
<td>&gt;2/3 upper limit of N serum LDH</td>
<td>&gt;0.45 upper limit of N serum LDH</td>
</tr>
</tbody>
</table>

Exudate = at least one criterion met

Transudative Pleural Effusions
- pathophysiology: alteration of systemic factors that affect the formation and absorption of pleural fluid (e.g. increased capillary hydrostatic pressure, decreased plasma oncotic pressure)
- etiology
  - CHF: usually right-sided or bilateral cirrhosis
  - nephrotic syndrome, protein losing enteropathy, cirrhosis
  - pulmonary embolism (may cause transudative but more often causes exudative effusion)
  - peritoneal dialysis, hypothyroidism, CF, urinothorax

Exudative Pleural Effusions
- pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction
- etiology (see Table 25)
Table 25. Exudative Pleural Effusion Etiologies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Parapneumonic effusion (associated with bacterial pneumonia, lung abscess)</td>
</tr>
<tr>
<td></td>
<td>Empyema (bacterial, fungal, TB)</td>
</tr>
<tr>
<td></td>
<td>TB pleuritis</td>
</tr>
<tr>
<td></td>
<td>Viral infection</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Lung carcinoma (35%)</td>
</tr>
<tr>
<td></td>
<td>Lymphoma (10%)</td>
</tr>
<tr>
<td></td>
<td>Metastases: breast (25%), ovary, kidney</td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Collagen vascular diseases: RA, SLE</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Post-CABG</td>
</tr>
<tr>
<td></td>
<td>Drug reaction</td>
</tr>
<tr>
<td>Intra-Abdominal</td>
<td>Subphrenic abscess</td>
</tr>
<tr>
<td></td>
<td>Pancreatic disease (elevated pleural fluid amylase)</td>
</tr>
<tr>
<td></td>
<td>Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumor)</td>
</tr>
<tr>
<td>Intra-Thoracic</td>
<td>Esophageal perforation (elevated fluid amylase)</td>
</tr>
<tr>
<td>Trauma</td>
<td>Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space due to trauma, tumor</td>
</tr>
<tr>
<td></td>
<td>Hemorrhax: rupture of a blood vessel, commonly by trauma or tumors</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax (spontaneous, traumatic, tension)</td>
</tr>
</tbody>
</table>

Signs and Symptoms
- often asymptomatic
- dyspnea: varies with size of effusion and underlying lung function
- pleuritic chest pain
- inspection: trachea deviates away from effusion, ipsilateral decreased expansion
- percussion: decreased tactile fremitus, dullness
- auscultation: decreased breath sounds, bronchial breathing and egophony at upper level, pleural friction rub

Investigations
- CXR
  - must have >200 mL of pleural fluid for visualization on PA film
  - lateral: >50 mL leads to blunting of posterior costophrenic angle
  - PA: blunting of lateral costophrenic angle
  - dense opacification of lung fields with concave meniscus
  - decubitus: fluid will shift unless it is loculated
  - supine: fluid will appear as general haziness
- thoracentesis: indicated if pleural effusion is a new finding; be sure to send off blood work (LDH, glucose, protein) at the same time for comparison
  - risk of re-expansion pulmonary edema if >1.5 L of fluid is removed
  - inspect for color, character, and odor of fluid
  - analyze fluid
- pleural biopsy: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology negative)
- ± U/S: detects small effusions and can guide thoracentesis
- treatment depends on cause, ± drainage if symptomatic
- CT can be helpful in differentiating parenchymal from pleural abnormalities

Table 26. Analysis of Pleural Effusion

<table>
<thead>
<tr>
<th>Measure</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, LDH</td>
<td>Transudate vs. exudate</td>
</tr>
<tr>
<td>Gram stain, Ziehl-Nielsen stain (TB), culture</td>
<td>Looking for specific organisms</td>
</tr>
<tr>
<td>Cell count differential</td>
<td>Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, serositis)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Malignancy, infection</td>
</tr>
<tr>
<td>Glucose (low)</td>
<td>RA, TB, empyema, malignancy, esophageal rupture</td>
</tr>
<tr>
<td>Rheumatoid factor, ANA, complement</td>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Amylase</td>
<td>Pancreatitis, esophageal perforation, malignancy</td>
</tr>
<tr>
<td>pH</td>
<td>Empyema &lt;7.2, TB, and mesothelioma &lt;7.3</td>
</tr>
<tr>
<td>Blood</td>
<td>Mostly traumatic, malignancy, PE with infarction, TB</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Chyllothorax from thoracic duct leakage, mostly due to trauma, lung CA, or lymphoma</td>
</tr>
</tbody>
</table>

Appearance of Pleural Fluid
- Bloody: trauma, malignancy
- White: chylothorax, empyema
- Black: aspergillosis, amoebic liver abscess
- Yellow-green: rheumatoid pleurisy
- Viscous: malignant mesothelioma
- Ammonia odor: urinothorax
- Food particles: esophageal rupture

Role of CT in Pleural Effusion
- To assess for fluid loculation, pleural thickening and nodules, parenchymal abnormalities and adenopathy
- Helps to distinguish benign from malignant effusion and transudative from exudative effusion
- May not distinguish empyema from parapneumonic effusion

Features of Malignant Effusion
- Multiple pleural nodules
- Nodular pleural thickening

Features of Exudative Effusion
- Loculation
- Pleural thickening
- Pleural nodules
- Extrapleural fat of increased density
Treatment
• thoracentesis
• treat underlying cause
• consider indwelling pleural catheter or pleurodesis in refractory effusions

Complicated Parapneumonic Effusion

• persistent bacteria in the pleural space but fluid is non-purulent
• neutrophils, pleural fluid acidos (pH <7.00), and high LDH
• often no bacteria grown since rapidly cleared from pleural space
• fibrin layer leading to loculation of pleural fluid
• treatment: antibiotics and drainage, treat as an empyema

Empyema

Definition
• pus in pleural space or an effusion with organisms seen on a Gram stain or culture (e.g. pleural fluid is grossly purulent)
• positive culture is not required for diagnosis

Etiology
• contiguous spread from lung infection (most commonly anaerobes) or infection through chest wall (e.g. trauma, surgery)

Signs and Symptoms
• fever, pleuritic chest pain

Investigations
• CT chest
• thoracentesis
• PMNs (lymphocytes in TB) ± visible organisms on Gram stain

Treatment
• antibiotic therapy for at least 4-6 wk (rarely effective alone)
• complete pleural drainage with chest tube
• if loculated, more difficult to drain – may require surgical drainage with video-assisted thorascopic surgery (VATS)

Atelectasis

• see General Surgery, GS10

Pneumothorax

Definition
• presence of air in the pleural space

Pathophysiology
• entry of air into pleural space raises intrapleural pressure causing partial lung deflation

Etiology
• traumatic: penetrating or non-penetrating chest injuries
• iatrogenic (central venous catheter, thoracentesis, mechanical ventilation with barotrauma)
• spontaneous (no history of trauma)
  ▪ primary (no underlying lung disease)
    ▪ spontaneous rupture of apical subpleural bleb of lung into pleural space
    ▪ predominantly tall, healthy, young males
  ▪ secondary (underlying lung disease)
    ▪ rupture of subpleural bleb which migrates along bronchioalveolar sheath to the mediastinum then to the intrapleural space
    ▪ necrosis of lung tissue adjacent to pleural surface (e.g. pneumonia, abscess, PCP, lung CA, emphysema)

Signs and Symptoms
• can be asymptomatic
• acute-onset pleuritic chest pain, dyspnea
• tachypnea, tachycardia
• tracheal deviation (contralateral deviation in tension pneumothorax)
• ipsilateral diminished chest expansion
• decreased tactile/vocal fremitus
• hyperresonance
• ipsilateral diminished breath sounds

**Investigations**
- CXR
  - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  - large: increased density and decreased volume of lung on side of pneumothorax
  - see Medical Imaging, MI8

**Treatment**
- small pneumothoraces (<20% with no signs of respiratory/circulatory collapse) resolve spontaneously; breathing 100% oxygen accelerates resorption of air
- small intercostal tube with Heimlich valve for most spontaneous pneumothoraces
- large pneumothoraces or those complicating underlying lung disease require placement of a chest tube connected to underwater seal ± suction
- for repeated episodes: pleurodesis with sclerosing agent or apical bullectomy and abrasion
- treat underlying cause (e.g. antibiotic for PCP)

## Asbestos-Related Pleural Disease and Mesothelioma

### Etiology and Pathophysiology
- benign manifestations of asbestos exposure
  - "benign asbestos pleural effusion"
    - exudative effusion, typically ~10 yr after exposure, resolves
    - pleural plaques, usually calcified
  - marker of exposure; usually an asymptomatic radiologic finding
- mesothelioma
  - primary malignancy of the pleura
  - decades after asbestos exposure (even with limited exposure)
  - smoking not a risk factor, but asbestos and smoking synergistically increase risk of lung cancer

### Signs and Symptoms
- persistent chest pain, dyspnea, cough, bloody pleural effusion, weight loss

### Investigations
- biopsy (pleuroscopic or open)
- needle biopsy may seed needle tract with tumor

### Treatment
- resection (extrapleural pneumonectomy) requires careful patient selection; rarely successful
  (average survival <1 yr)

## Respiratory Failure

### Definition
- failure of respiratory system to maintain normal blood gases
- hypoxemic ($P_{O_2} < 60$ mmHg)
- hypercapnic ($P_{CO_2} > 50$ mmHg)
- acute vs. chronic (compensatory mechanisms activated)

### Signs and Symptoms
- signs of underlying disease
- hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale
- hypercapnia: headache, dyspnea, drowsiness, asterixis, warm periphery, plethora, increased ICP
  (secondary to vasodilatation)

### Investigations
- serial ABGs
- CXR and/or CT, bronchoscopy to characterize underlying cause if unclear
Hypoxemic Respiratory Failure

Definition
• $P_aO_2$ decreased, $P_aCO_2$ normal or decreased

Treatment
• reverse the underlying pathology
• oxygen therapy: maintain oxygenation (if shunt present, supplemental $O_2$ is less effective; see Anesthesia, A9, for oxygen delivery systems)
• ventilation, BiPAP and PEEP/CPAP (see Anesthesia, A10): positive pressure can recruit alveoli and redistribute lung fluid
• improve cardiac output: ± hemodynamic support (fluids, vaspressors, inotropes), reduction of $O_2$ requirements

Table 27. Approach to Hypoxemia

<table>
<thead>
<tr>
<th>Type of Hypoxemia</th>
<th>Settings</th>
<th>$P_aCO_2$</th>
<th>A-aDO2</th>
<th>Oxygen Therapy</th>
<th>Ventilation, BiPAP and PEEP</th>
<th>Improved Cardiac Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low FIO2</td>
<td>Postop, high altitude</td>
<td>N or ↓</td>
<td>N</td>
<td>Improves</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>2. Hypoventilation</td>
<td>Drug overdose</td>
<td>↑</td>
<td>N</td>
<td>Improves</td>
<td>Improves with ventilation</td>
<td>No change</td>
</tr>
<tr>
<td>3a. Shunt</td>
<td>ARDS, pneumonia</td>
<td>N or ↓</td>
<td>↑</td>
<td>No change</td>
<td>Improves (except if one-sided)</td>
<td>Improves</td>
</tr>
<tr>
<td>3b. Shunt (Right to Left)</td>
<td>Pulmonary HTN</td>
<td>N or ↓</td>
<td>↑</td>
<td>No change</td>
<td>Worsens</td>
<td>Worsens</td>
</tr>
<tr>
<td>4. Low Mixed Venous $O_2$ Content</td>
<td>Shock</td>
<td>↓</td>
<td>↑</td>
<td>Improves or no change</td>
<td>Worsens</td>
<td>Improves</td>
</tr>
<tr>
<td>5. V/Q Mismatch</td>
<td>COPD</td>
<td>N or ↑</td>
<td>↑</td>
<td>Improves (small amounts)</td>
<td>Often improves</td>
<td>Improves</td>
</tr>
<tr>
<td>6. Diffusion Impairment</td>
<td>ILD, emphysema</td>
<td>N</td>
<td>↑</td>
<td>Improves</td>
<td>Improves with positive pressure</td>
<td>No change or worsens</td>
</tr>
</tbody>
</table>

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Hypercapnic Respiratory Failure

• $P_aCO_2$ increased, $P_aO_2$ decreased

Pathophysiology
• increased $CO_2$ production: fever, sepsis, seizure, acidosis, carbohydrate load
• alveolar hypoventilation: COPD, asthma, CF; chest wall disorder, dead space ventilation (rapid shallow breathing)
  • inefficient gas exchange results in inadequate $CO_2$ removal in spite of normal or increased minute volume
• hypoventilation
  • central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (opiates, benzodiazepines)
  • neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis, kyphoscoliosis
  • muscle fatigue

Treatment
• reverse the underlying pathology
• if $P_aCO_2$ >50 mmHg and pH is acidemic consider noninvasive or mechanical ventilation
• correct exacerbating factors
  • NTT/ETT suction: clearance of secretions
  • bronchodilators: reduction of airway resistance
  • antibiotics: treatment of infections
• maintain oxygenation (see above)
• diet: increased carbohydrate can increase $P_aCO_2$ in those with mechanical or limited alveolar ventilation; high lipids decrease $P_aCO_2$

Dead Space
• Ventilation without perfusion
• The opposite of shunt

Causes of Hypercapnia
• High Inspired $CO_2$
• Low Total Ventilation
• High Deadspace Ventilation
• High $CO_2$ Production

In chronic hypercapnia, supplemental $O_2$ may decrease the hypoxic drive to breathe, but do not deny oxygen if the patient is hypoxic

In COPD patients with chronic hypercapnia ("$CO_2$ retainers"), provide supplemental oxygen to achieve target $SaO_2$ from 88-92%
Acute Respiratory Distress Syndrome

• clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
• The Berlin Criteria (JAMA 2012; 307:2526-2533) for ARDS
  ➢ acute onset
    • within 7 d of a defined event, such as sepsis, pneumonia, or patient noticing worsening of respiratory symptoms
      ➢ usually occurs within 72 h of presumed trigger
    • bilateral opacities consistent with pulmonary edema on either CT or CXR
    • not fully explained by cardiac failure/fluid overload, but patient may have concurrent heart failure
    • an objective assessment (e.g. echocardiogram) should be performed if no clear risk factors

Etiology
• direct lung injury
  ➢ airway: aspiration (gastric contents, drowning), pneumonia, inhalation injury (oxygen toxicity, nitrogen dioxide, smoke)
  ➢ circulation: embolism (fat, amniotic fluid), reperfusion injury
• indirect lung injury
  ➢ circulation: sepsis, shock, trauma, blood transfusion, pancreatitis
  ➢ neurogenic: head trauma, intracranial hemorrhage, drug overdose (narcotics, sedatives, TCAs)

Pathophysiology
• disruption of alveolar capillary membranes → leaky capillaries → interstitial and alveolar pulmonary edema → reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN

Clinical Course
A. Exudative Phase
• first 7 d of illness after exposure to ARDS precipitant
• alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
• patients develop dyspnea, tachypnea, increased work of breathing
  ➢ these result in respiratory fatigue and eventually respiratory failure (see Hypoxemic Respiratory Failure, R26)

B. Fibroproliferative Phase
• after day 7
• may still experience dyspnea, tachypnea, fatigue, and hypoxemia
• most patients clinically improve and are able to wean off mechanical ventilation
• some patients develop fibrotic lung changes that may require long-term support on supplemental oxygen or even mechanical ventilation
• if fibrosis present, associated with increased mortality

Treatment
• based on ARDS network (see Landmark Respirology Trials, R36)
• treat underlying disorder (e.g. antibiotics if infection present)
• mechanical ventilation using low tidal volumes (<6 mL/kg) to prevent barotrauma
  ➢ use optimal amount of PEEP (positive end-expiratory pressure) to keep airways open and allow the use of lower F(IO2)
  ➢ may consider using prone ventilation, and/or inhaled nitric oxide, high frequency oscillator or ECMO (extracorporeal membrane oxygenation) if conventional treatment is failing
• fluids and inotropic therapy (e.g. dopamine, vasopressin) if cardiac output inadequate
• pulmonary-arterial catheter now seldom used for monitoring hemodynamics
• mortality: 30–40%, usually due to non-pulmonary complications
• sequelae of ARDS include residual pulmonary impairment, severe debilitation, polyneuropathy and psychologic difficulties, which gradually improve over time
• most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity
Neoplasms

Lung Cancer

Classification
- Lung tumors can be classified as primary or secondary, benign or malignant, endobronchial or parenchymal
- Bronchogenic carcinoma (epithelial lung tumors) are the most common type of primary lung tumor (other types make up less than 1%)
  - Small cell lung cancer (SCLC)
  - Non-small-cell lung cancer (NSCLC)
- Squamous cell carcinoma: arise from the proximal respiratory epithelium
- Adenocarcinoma: incidence is increasing; most common subtype in nonsmokers
  - Bronchoalveolar carcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring
- Large cell undifferentiated cancer: diagnosis of exclusion
- Benign epithelial lung tumors can be classified as papillomas or adenomas

Table 28. Characteristics of Bronchogenic Cancer

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Incidence</th>
<th>Correlation with Smoking</th>
<th>Location</th>
<th>Histology</th>
<th>Metastasis</th>
<th>5 Year Survival Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>M: 35%; F: 40%</td>
<td>Weak</td>
<td>Peripheral</td>
<td>Glandular, mucin producing</td>
<td>Early, distant</td>
<td>12% (60% for bronchoalveolar carcinoma, a subtype, with a resectable solitary lesion)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma (SCC)</td>
<td>30%</td>
<td>Strong</td>
<td>Central</td>
<td>Keratin, intercellular bridges</td>
<td>Local invasion and distant spread, may cavitate</td>
<td>25%</td>
</tr>
<tr>
<td>SCLC</td>
<td>25%</td>
<td>Strong</td>
<td>Central</td>
<td>Oat cell, neuroendocrine</td>
<td>Disseminated at presentation Origin in endobronchial cells</td>
<td>1% (poorest prognosis)</td>
</tr>
<tr>
<td>Large Cell Carcinoma</td>
<td>10-15%</td>
<td>Strong</td>
<td>Peripheral</td>
<td>Anaplastic, undifferentiated</td>
<td>Early, distant</td>
<td>13%</td>
</tr>
</tbody>
</table>

Risk Factors
- Cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers
- Other risk factors include cigar smoking, pipe smoking, second-hand smoke, asbestos without smoking (relative risk is 5), asbestos with smoking (relative risk is 92), metals (e.g., chromium, arsenic, nickel), radon gas, ionizing radiation, genetics

Signs and Symptoms
- May be due to primary lesion, metastasis, or paraneoplastic syndrome
- Primary lesion
  - Cough (75%): beware of chronic cough that changes in character
  - Dyspnea (60%)
  - Chest pain (45%)
  - Hemoptysis (35%)
  - Other pain (25%)
  - Clubbing (21%)
  - Constitutional symptoms: anorexia, weight loss, fever, anemia
- Metastasis
  - Lung, hilum, mediastinum, pleura: pleural effusion, atelectasis, wheezing
  - Pericardium: pericarditis, pericardial tamponade
  - Esophageal compression: dysphagia
  - Phrenic nerve: paralyzed diaphragm
  - Recurrent laryngeal nerve: hoarseness
  - Superior vena cava syndrome
  - Obstruction of SVC causing neck and facial swelling, as well as dyspnea and cough
  - Other symptoms: hoarseness, tongue swelling, epistaxis, and hemoptysis
  - Physical findings: dilated neck veins, increased number of collateral veins covering the anterior chest wall, cyanosis, edema of the face, arms, and chest, Pemberton’s sign (facial flushing, cyanosis, and distension of neck veins upon raising both arms above head)
  - Milder symptoms if obstruction is above the azygos vein
  - Lung apex (Pancoast tumor): Horner’s syndrome, brachial plexus palsy (most commonly C8 and T1 nerve roots)
  - Rib and vertebrae: erosion
  - Distal metastasis to brain, bone, liver, adrenals
- Paraneoplastic syndromes
  - A group of disorders associated with malignant disease, not related to the physical effects of the tumor itself
  - Most often associated with SCLC

Summary of Recommendations on Screening for Lung Cancer
- American College of Chest Physicians (2013)
  - Screening with CT
    - Not recommended
  - Screening with low-dose CT
    - Recommended for high-risk patients (current or former smokers within the last 15 yr, aged 55-74; >30 pack yr smoking Hx)
- American Lung Association (2013)
  - Screening with CXR
    - Not recommended
  - Screening with Low-Dose CT
    - Recommended for high-risk patients (current or former smokers aged 55-74, >30 pack yr smoking Hx, no Hx of lung cancer)

Reduced Lung Cancer Mortality with Low-Dose CT Screening
- NEJM 2011;365:395-409
- Study: Multicenter RCT.
- Methods: 53,454 participants at high risk for lung cancer (55-74 yr; >30 smoking index; current or former smokers quit within the last 15 yr) were assigned to undergo three annual screenings with either low dose CT or single-view PA CXR.
- Results: A relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95% CI 6.6-28.7; p=0.004). Rate of death from any cause was reduced in the low-dose CT group as compared to the CXR group by 8.7% (95% CI 1.2-13.6; p=0.02).

| Low-dose CT: CXR |
|------------------|-----------------|
| Rate of death    | 24.2%           |
| False positives  | 96.4%           |
| Incidence of lung cancer | 645/100 K person yr |
| Deaths from lung cancer | 247/100 K person yr |

Conclusions: Screening with low-dose CT reduces mortality from lung cancer

Malignant lung tumors are the most common cause of cancer mortality throughout the world in both men and women

Endobronchial Ultrasound (EBUS)
- Allows visualization of peri-bronchial structures and distal peripheral lung lesions
- Provides detailed assessment of the airway wall layers
- Allows for guided biopsies of lymph nodes and tumors
- Used for diagnosis and staging
Table 29. Paraneoplastic Syndromes

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Presentation</th>
<th>Associated Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td>Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Acanthosis nigricans, Dermatomyositis</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypercalcemia (osteolytic or PTHrP)</td>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Cushing’s syndrome (ACTH)</td>
<td>SCLC</td>
</tr>
<tr>
<td></td>
<td>Somatostatinoma syndrome</td>
<td>Bronchial carcinoid</td>
</tr>
<tr>
<td></td>
<td>SIADH</td>
<td></td>
</tr>
<tr>
<td>Neuromyopathic</td>
<td>Lambert-Eaton syndrome, Polymyositis</td>
<td>SCLC</td>
</tr>
<tr>
<td></td>
<td>Subacute cerebellar degeneration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spino-cerebellar degeneration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td></td>
</tr>
<tr>
<td>Vascular/Hematologic</td>
<td>Nonbacterial endocarditis, Thrombophlebitis</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td></td>
<td>Trousseau’s syndrome (migratory)</td>
<td>NSCLC</td>
</tr>
<tr>
<td></td>
<td>DIC</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
- initial diagnosis
  - imaging: CXR, CT chest + upper abdomen, PET scan, bone scan
  - cytology: sputum
  - biopsy: bronchoscopy, EBUS, CT-guided percutaneous needle biopsy, mediastinoscopy
- staging workup
  - TMN staging system: T - primary tumor (size); N - regional lymph nodes; M - distant metastasis
  - blood work: electrolytes, LFTs, calcium, ALP
  - imaging: CXR, CT thorax and upper abdomen, bone scan, neuroimaging
  - invasive: bronchoscopy (EBUS), mediastinoscopy, mediastinotomy, thoracotomy
  - screen adenocarcinoma for EGFR mutations

Table 30. SCLC vs. NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Treatment</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited</td>
<td>Confined to single radiation port (one hemithorax and regional lymph nodes)</td>
<td>Radiation ± chemotherapy with prophylactic to brain (12 wk without treatment)</td>
<td>1-2 yr</td>
</tr>
<tr>
<td>Extensive</td>
<td>Extension beyond a single radiation port</td>
<td>Chemotherapy</td>
<td>6 mo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Treatment</th>
<th>5 Yr Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>T1a-T1bNO0M0</td>
<td>1st line is complete surgical resection with possible post-operative adjuvant chemotherapy for stage IA and stage IB</td>
<td>50-73</td>
</tr>
<tr>
<td>IB</td>
<td>T2aNO0M0</td>
<td>-radiotherapy for non-surgical candidates</td>
<td>43-58</td>
</tr>
<tr>
<td>IIA</td>
<td>T1a-T2a,N1M0 or T2bNO0M0</td>
<td>Combined modality approach (concurent chemotherapy followed by surgery)</td>
<td>36-46</td>
</tr>
<tr>
<td>IIB</td>
<td>T2bN1M0 or T3N0M0</td>
<td></td>
<td>25-36</td>
</tr>
<tr>
<td>IIIA</td>
<td>T1a-T2bN2M0 or T3N1-2M0 or T4N0-1M0</td>
<td></td>
<td>19-24</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4N2M0 or T1-4N3M0</td>
<td></td>
<td>7-9</td>
</tr>
<tr>
<td>IV</td>
<td>T1-4N0-3M1a-1b</td>
<td>Systemic therapy or molecularly targeted therapy or symptom-based palliative management (radiation); isolated metastasis may be resected</td>
<td>2-13</td>
</tr>
</tbody>
</table>

* Depends on clinical vs. pathologic stage

Refer to AJCC Cancer Staging Manual, 7th ed. (2010) for complete TNM classification

Treatment
- options include surgery, radiotherapy, chemotherapy, and palliative care for end-stage disease
- surgery not usually performed for SCLC since it is generally non-curably
- contraindications for surgery
  - spread to contralateral lymph nodes or distant sites
  - patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases
  - poor pulmonary status (e.g. unable to tolerate resection of lung)

Horner has a MAP of the Coast
A Pancoast tumor compresses the cervical sympathetic plexus causing a Horner’s syndrome:
- Miosis
- Anhidrosis
- Ptosis

Prevention
- Smoking cessation
- Avoidance of exposures
- Early detection
• chemotherapy (used in combination with other treatments)
  ▪ common agents: etoposide, platinum agents (e.g. cisplatinum), ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  ▪ complications
    • acute: tumor lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
    • chronic: neurologic damage, leukemia, additional primary neoplasms

Approach to the Solitary Pulmonary Nodule

• see Medical Imaging, MI7

Definition
• a round or oval, sharply circumscribed radiographic lesion up to 3-4 cm, which may or may not be calcified, and is surrounded by normal lung
• can be benign or malignant

Table 31. Differential Diagnosis for Benign vs. Malignant Solitary Nodule

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Benign (70%)</th>
<th>Malignant (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;3 cm, round, regular</td>
<td>&gt;3 cm, irregular, spiculated</td>
</tr>
<tr>
<td>Margins</td>
<td>Smooth margin</td>
<td>Ill-defined or notched margin</td>
</tr>
<tr>
<td>Features</td>
<td>Calcified pattern: central, “popcorn” pattern if hamartoma, usually no cavitation; if cavitating, wall is smooth and thin, no other lung pathology</td>
<td>Usually not calcified; if calcified, pattern is eccentric, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>Doubles in &lt;1 mo or &gt;2 yr</td>
<td>Doubles in &gt;1 mo or &lt;2 yr</td>
</tr>
</tbody>
</table>

Investigations)
• CXR: always compare with previous CXR
• CT densitometry and contrast enhanced CT of thorax
• sputum cytology: usually poor yield
• biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy or thoracotomy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  • if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  • if a biopsy is non-diagnostic, whether to observe, re-biopsy, or resect will depend on the level of suspicion
• watchful waiting: repeat CXR and/or CT scan at 3, 6, 12 mo
• PET scan can help distinguish benign from malignant nodules

Table 32. CXR Characteristics of Benign vs. Malignant Solitary Nodule

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;3 cm, round, regular</td>
<td>&gt;3 cm, irregular, spiculated</td>
</tr>
<tr>
<td>Margins</td>
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<td>Usually not calcified; if calcified, pattern is eccentric, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>Doubles in &lt;1 mo or &gt;2 yr</td>
<td>Doubles in &gt;1 mo or &lt;2 yr</td>
</tr>
</tbody>
</table>
### Sleep-Related Breathing Disorders

#### Hypoventilation Syndromes

- primary alveolar hypoventilation: idiopathic
- obesity-hypoventilation syndrome (Pickwickian syndrome)
- respiratory neuromuscular disorders

#### Sleep Apnea

**Definition**
- episodic decreases in airflow during sleep
- quantitatively measured by the Apnea/Hypopnea Index (AHI) = # of apneic and hypopneic events per hour of sleep
- sleep apnea generally accepted to be present if AHI >15

**Classification**
- obstructive (OSA)
  - caused by transient, episodic obstruction of the upper airway
  - absent or reduced airflow despite persistent respiratory effort
- central (CSA) (see Neurology, N46)
  - caused by transient, episodic decreases in CNS drive to breathe
  - no airflow because no respiratory effort
  - Cheyne-Stokes Respiration: a form of CSA in which central apneas alternate with hyperpneas to produce a crescendo–decrescendo pattern of tidal volume; seen in severe LV dysfunction, brain injury, and other settings (see Figure 2)
- mixed (MSA)
  - features of both OSA and CSA
  - loss of hypoxic and hypercapnic drives to breathe secondary to "resuscitative breathing": overcompensatory hyperventilation upon awakening from OSA induced hypoxia

**Risk Factors**
- for OSA: obesity, upper airway abnormality, neuromuscular disease, hypothyroidism, alcohol/sedative use, nasal congestion, sleep deprivation
- for CSA: LV failure, brainstem lesions, encephalitis, encephalopathy, myxedema, high altitude

**Signs and Symptoms**
- obtain history from spouse/partner
- secondary to repeated arousals and fragmentation of sleep: daytime somnolence, personality and cognitive changes, snoring
- secondary to hypoxemia and hypercapnia: morning headache, polycythemia, pulmonary/systemic HTN, cor pulmonale/CHF, nocturnal angina, arrhythmias

---

![Solitary pulmonary nodule](image)

**Figure 12. Evaluation of a solitary pulmonary nodule**

<table>
<thead>
<tr>
<th>Significant risk factor on Hx</th>
<th>Check previous CXR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Looks malignant or changed</td>
<td></td>
</tr>
<tr>
<td>Looks benign or unchanged</td>
<td></td>
</tr>
<tr>
<td>Repeat CXR in 3-6 months</td>
<td></td>
</tr>
<tr>
<td>CT thorax</td>
<td>Repeat CXR every 6 months x 1 year</td>
</tr>
<tr>
<td>Infection</td>
<td>Observe</td>
</tr>
<tr>
<td>Cancer</td>
<td>Stage and treat</td>
</tr>
<tr>
<td>Calcification</td>
<td>Observe</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>PET scan</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Transbronchial needle biopsy</td>
</tr>
<tr>
<td>Still no diagnosis ± growing</td>
<td>Observe</td>
</tr>
<tr>
<td>Cancer</td>
<td>Stage and treat</td>
</tr>
<tr>
<td>Stage and treat</td>
<td>Observe</td>
</tr>
</tbody>
</table>

---

Normal Respiratory Changes during Sleep
- Tidal volume decreases
- Arterial CO₂ increases (due to decreased minute ventilation)
- Pharyngeal dilator muscles relax causing increased upper airway resistance

Apnea: absence of breathing for ≥10 s
Hypopnea: excessive decrease in rate or depth of breathing (>50% reduction in ventilation)
Hyperpnea: excessive increase in rate or depth of breathing
• the typical presentation for OSA is a middle-aged obese male who snores
• CSA can be due to neurological disease

**Investigations**

- sleep study (polysomnography)
  - evaluates sleep stages, airflow, ribcage movement, ECG, SaO₂, limb movements
  - indications
    - excessive daytime sleepiness
    - unexplained pulmonary HTN or polycythemia
    - daytime hypercapnia
    - titration of optimal nasal CPAP
    - assessment of objective response to other interventions

**Treatment**

- modifiable factors: weight loss, decreased alcohol/sedatives, nasal decongestion, treatment of underlying medical conditions
- OSA or MSA: nasal CPAP, postural therapy (e.g. no supine sleeping), dental appliance, uvulopalatopharyngoplasty, tonsillectomy
- CSA or hypoventilation syndromes: nasal BiPAP/CPAP, respiratory stimulants (e.g. progesterone) in select cases
- tracheostomy rarely required and should be used as last resort for OSA

**Complications**

- depression, weight gain, decreased quality of life, workplace and vehicular accidents, cardiac complications (e.g. HTN), reduced work/social function

---

**Introduction to Intensive Care**

- goal is to provide stabilization for critically ill patients: hemodynamic, respiratory or cardiac instability, or need for close monitoring

**Intensive Care Unit Basics**

**Lines and Catheters**

- arterial lines
  - monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs
  - common sites are the radial and femoral arteries
- central venous catheter (central line)
  - administer IV fluids, monitor CVP, insert pulmonary artery catheters
  - administer TPN and agents too irritating for peripheral line
  - common sites: internal jugular vein, subclavian vein, femoral vein
- pulmonary arterial catheter
  - balloon guides the catheter from a major vein to the right heart
  - measures pulmonary capillary wedge pressure (PCWP) via a catheter wedged in distal pulmonary artery
  - PCWP reflects the LA and LV diastolic pressure (barring pulmonary venous or mitral valve disease)
  - indications (now used infrequently due to associated complications)
    - diagnosis of shock states, primary pulmonary HTN, valvular disease, intracardiac shunts, cardiac tamponade, PE
    - assessment of hemodynamic response to therapies
    - differentiation of high- vs. low-pressure pulmonary edema
    - management of complicated MI, multiorgan system failure and/or severe burns, or hemodynamic instability after cardiac surgery
  - absolute contraindications
    - tricuspid or pulmonary valve mechanical prosthesis
    - right heart mass (thrombus or tumor)
    - tricuspid or pulmonary valve endocarditis

**Table 33. Useful Equations and Cardiopulmonary Parameters**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA = (Ht (cm) + Wt (kg) – 60)/100</td>
<td>Body surface area</td>
</tr>
<tr>
<td>SV = CO / HR</td>
<td>Cardiac output</td>
</tr>
<tr>
<td>Cl = CO / BSA</td>
<td>Stroke index</td>
</tr>
<tr>
<td>RV Ejection Fraction = SV / RVEDV</td>
<td>Right ventricular ejection fraction</td>
</tr>
<tr>
<td>SVRI = (MAP – RAP) 80/Cl</td>
<td>Systemic vascular resistance index</td>
</tr>
<tr>
<td>PP = sBP – dBP</td>
<td>Pulse pressure</td>
</tr>
<tr>
<td>MAP = 1/3 sBP + 2/3 dBP + 1/3 PP</td>
<td>Mean arterial pressure</td>
</tr>
</tbody>
</table>

**BSA** = body surface area; **CO** = cardiac output; **dBP** = diastolic blood pressure; **HR** = heart rate; **LVEDP** = left ventricular end diastolic pressure; **MAP** = mean arterial pressure; **PCWP** = pulmonary capillary wedge pressure; **PP** = pulse pressure; **RAP** = right atrial pressure; **RVEDV** = right ventricular end diastolic volume; **sBP** = systolic blood pressure; **SV** = stroke volume; **SVI** = stroke volume index; **SVRI** = systemic vascular resistance index
Organ Failure

Table 34. Types of Organ Failure

<table>
<thead>
<tr>
<th>Type of Failure (see Respiratory Failure, R25)</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Failure</td>
<td>Hypoxemia</td>
<td>Treat underlying cause (e.g. lung disease, shunt, V/Q mismatch, drug-related, cardiac)</td>
</tr>
<tr>
<td></td>
<td>Hypercapnea</td>
<td>Manage mechanical ventilation settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supplemental oxygen</td>
</tr>
<tr>
<td>Cardiac Failure (see Cardiology and Cardiac Surgery, C33)</td>
<td>Hypotension Decreased urine output Altered mental status Arrhythmia Hypoxia</td>
<td>Treat underlying cause (e.g. bradycardia, tachycardia, blood loss, cardiac insufficiency) Volume resuscitation Vasopressors Inotropes aortic balloon pump</td>
</tr>
<tr>
<td>Coagulopathy (see Hematology, H32)</td>
<td>Increased INR or PTT Low platelet count Bleeding, bruising</td>
<td>Treat underlying cause (e.g. thrombocytopenia, drug-related, immune-related, DIC) Transfusion of blood product, clotting factors</td>
</tr>
<tr>
<td>Liver Failure (see Gastroenterology, G36)</td>
<td>Elevated transaminases, bilirubin Jaundice Mental alteration (encephalopathy) Hyponcavsmia</td>
<td>Treat underlying cause (e.g. viral hepatitis, drug related, metabolic) Liver transplant Lactulose</td>
</tr>
<tr>
<td>Renal Failure (see Nephrology, NP35)</td>
<td>Elevated creatinine Reduced urine output Signs of volume overload (e.g. CHF, effusions)</td>
<td>Treat underlying cause (e.g. shock, drug-related, obstruction) Correct volume and electrolyte status, eliminate toxins</td>
</tr>
</tbody>
</table>

Shock

- See Emergency Medicine, ER3
- Inadequate tissue perfusion potentially resulting in end organ injury
  - Categories of shock:
    - Hypovolemic: hemorrhage, dehydration, vomiting, diarrhea, interstitial fluid redistribution
    - Cardiogenic: myopathic (myocardial ischemia ± infraction), mechanical, arrhythmic, pharmacologic
    - Obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
    - Distributive: sepsis, anaphylactic reaction, neurogenic, endocrinologic, toxic

Table 35. Changes Seen in Different Classes of Shock

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Obstructive</th>
<th>Distributive</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>↑</td>
<td>↑, N, or ↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>BP</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>JVP</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Extremities</td>
<td>Cold</td>
<td>Cold</td>
<td>N or Cold</td>
<td>Warm</td>
</tr>
<tr>
<td>Other</td>
<td>Look for visible hemorrhage or signs of dehydration</td>
<td>Bilateral crackles on chest exam</td>
<td>Depending on cause, may see pulsus paradoxus, Kussmaul’s sign, or tracheal deviation</td>
<td>Look for obvious signs of infection or anaphylaxis</td>
</tr>
</tbody>
</table>

Sepsis

- The leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- The predominant theory is that sepsis is attributable to uncontrollable immune system activation

Definitions

- Sepsis: the presence of both infection and SIRS (see Table 36)
- Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension
- Septic shock: sepsis with arterial hypotension despite adequate fluid resuscitation

Intensive Insulin Therapy in Critically Ill Patients

Study: Prospective, randomized controlled clinical outcome study

Patients: 1,546 patients admitted to the ICU

Intervention: At admission, patients were randomly assigned to either intensive insulin therapy or conventional therapy. Those in the intensive group had an infusion started if BG exceeded 6.1 mEq/L, and maintained to keep BG between 4.4-6.1 mEq/L. Those in the conventional group were started on insulin only if BG exceeded 11.9, and the infusion was adjusted for a target between 10.0-11.1 mEq/L.

Primary Outcome: Death from any cause during ICU stay.

Results: 35 patients (4.6%) died in the intensive group in the ICU, vs. 63 patients (8.0%) in the conventional group. This represents a 32% mortality reduction (p=0.04). Intensive insulin therapy also reduced overall in-hospital mortality, lowered deaths due to sepsis, multi-organ failure. Most of the mortality benefit was seen in long stay patients (>5 d).

Conclusion: Intensive insulin therapy in the ICU reduces mortality by 32%, and improves in-hospital mortality and morbidity.

Shock: Clinical Correlation

Hypovolemic: patients have cool extremities due to peripheral vasoconstriction
Cardiogenic: patients usually have signs of left-sided heart failure
Obstructive: varied presentation
Distributive: patients have warm extremities due to peripheral vasodilation

Causes of SHOCK

Spinal (neurogenic), Septic

Hemorrhagic Obstructive (e.g. tension pneumothorax, cardiac tamponade, PE)
Cardiogenic (e.g. arrhythmia, MI)
Anaphylactic

Systemic Inflammatory Response Syndrome (SIRS): generalized inflammatory reaction caused by infectious and noninfectious entities, manifested by the following criteria:
- Body temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or P CO2 <32 mmHg
- WBC >12,000 cells/mL or <4,000 cells/mL or >10% bands
• multiorgan dysfunction syndrome: sepsis in the presence of altered organ function such that homeostasis cannot be maintained without intervention

Signs and Symptoms

<table>
<thead>
<tr>
<th>General Variables</th>
<th>Organ Dysfunction Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (&gt;38°C) or hypothermia (&lt;36°C)</td>
<td>Arterial hypoxemia (P_{aO2}/F_{iO2} &lt;300)</td>
</tr>
<tr>
<td>Heart rate &gt;90/min</td>
<td>Acute oliguria (urine output &lt;0.5 mL/kg/h)</td>
</tr>
<tr>
<td>SBP &lt;90 mmHg, MAP &lt;70, or a SBP decrease &gt;40 mmHg</td>
<td>Creatinine increase &gt;40 mg/dL</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Congestion abnormalities (INR &gt;1.5 or aPTT &gt;60 s)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Ileus (absent bowel sounds)</td>
</tr>
<tr>
<td>Positive fluid balance (&gt;20 mL/kg over 24 h)</td>
<td>Thrombocytopenia (platelet count &lt;100,000/L)</td>
</tr>
<tr>
<td>Hyperglycemia (BG &gt;140 mg/dL) in the absence of diabetes</td>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;4 mg/dL)</td>
</tr>
<tr>
<td>Leukopenia (WBC &lt;4,000/L)</td>
<td>Leukocytosis (WBC &gt;12,000/L)</td>
</tr>
<tr>
<td>Normal WBC count with &gt;10% immature forms</td>
<td>Tissue Perfusion Variables</td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;2 SD above the normal value</td>
<td>Hyperlactatemia (&gt;20 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>Decreased capillary refill or mottling</td>
</tr>
</tbody>
</table>


Treatment

• identify the cause and source of infection: blood, sputum, urine Gram stain and C&S

• initiate empiric antibiotic therapy

• monitor, restore and maintain hemodynamic function

Early Goal Directed Therapy

• adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with demand

• should be started immediately and completed within 6 h of recognition of severe sepsis or septic shock

• patient should meet SIRS criteria and SBP <90 mmHg or lactate >40 mmHg

• monitor, restore and maintain hemodynamic function

• initiate empiric antibiotic therapy

• identify the cause and source of infection: blood, sputum, urine Gram stain and C&S

• early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier

• control hyperglycemia with insulin to decrease infectious complications

• physiologic dose corticosteroid replacement therapy in patients with relative adrenal insufficiency (nonresponders to corticotropin stimulation test)

• consider in mechanically ventilated septic shock patients with organ dysfunction requiring vasopressors, despite early goal-directed therapy and appropriate antibiotic therapy

• recombinant activated protein C may be considered in patients with severe sepsis or septic shock with an APACHE II score >25 despite early goal-directed therapy and appropriate antibiotic therapy

• DVT/PE prophylaxis

• advanced care planning, including the communication of likely outcomes and realistic goals of treatment with patients and families
**Table 37. Common Medications for Respiratory Diseases**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β₂-AGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td>salbutamol/albuterol (Ventolin®) (light blue/navy), terbutaline (Bricanyl®)</td>
<td>1-2 puffs q4-6h prn</td>
<td>Bronchodilator in acute reversible airway obstruction</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td>salmeterol (Serevent®), formoterol (Foradil®), indacaterol (Arcapta Neohaler®)</td>
<td>1-2 puffs bid</td>
<td>Maintenance treatment (prevention of bronchospasm) in COPD, asthma</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>fluticasone and salmeterol (Advair®) (blue MDI)</td>
<td>1 puff bid</td>
<td>COPD and asthma</td>
</tr>
<tr>
<td><strong>ANTICHOLINERGICS</strong></td>
<td>ipratropium bromide (Atrovent®) (clear/green), tiotropium bromide (Spiriva®), glycopyrronium bromide</td>
<td>2-3 puffs qid</td>
<td>Bronchodilator used in COPD, bronchitis and emphysema</td>
</tr>
<tr>
<td><strong>CORTICOSTEROIDS</strong></td>
<td>Inhaled</td>
<td>fluticasone (Fvent®) (orange/peach), budesonide (Pulmicort®), ciclesonide (Alvesco®), beclomethasone (QVAR®, Vanceril®), mometasone (Asmanex®)</td>
<td>2-4 puffs bid</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td>prednisone (Deltasone®)</td>
<td>Typically 40-60 mg per day PO 125 mg q8h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q6h for 5 d</td>
<td>Acute exacerbation of COPD; severe, persistent asthma, PCP Status asthmaticus</td>
</tr>
<tr>
<td><strong>ADJUNCT AGENTS</strong></td>
<td>theophylline (Uniphyll®)</td>
<td>400-800 mg DD</td>
<td>Treatment of symptoms of reversible airway obstruction due to COPD</td>
</tr>
<tr>
<td><strong>LEUKOTRIENE ANTAGONISTS</strong></td>
<td>montelukast (Singular®)</td>
<td>10 mg PO qhs, now only available as once daily slow release 20 mg bid</td>
<td>Prophylaxis and chronic treatment of asthma</td>
</tr>
<tr>
<td><strong>MONOCLONAL ANTIBODIES</strong></td>
<td>omalizumab (Xolair®)</td>
<td>150-375 mg SC q2-4wk</td>
<td>Moderate-severe persistent asthma</td>
</tr>
<tr>
<td><strong>PDE5 INHIBITORS</strong></td>
<td>ralfuslax (Dairex®)</td>
<td>500 µg PO DD</td>
<td>Severe emphysema, with frequent exacerbations</td>
</tr>
<tr>
<td><strong>ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA</strong></td>
<td>Macrolide</td>
<td>erythromycin</td>
<td>250-500 mg PO bid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td>azithromycin</td>
<td>500 mg PO x 1 dose, then 250 mg OD x 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td>500 mg PO bid x 7-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>100 mg PO bid x 7-10 d</td>
<td>Alternate to macrolide or fluoroquinolone</td>
</tr>
<tr>
<td></td>
<td>Fluoroquinolone</td>
<td>levofloxacin (Levaquin®)</td>
<td>500 mg PO OD x 7-10 d</td>
</tr>
</tbody>
</table>
### Table 37. Common Medications for Respiratory Diseases (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd gen Cephalosporin</td>
<td>ceftriaxone (Rocephin®) 1-2 g IV OD x 7-10 d</td>
<td>Combine with fluoroquinolone or macrolide</td>
<td>Rash, diarhoea, eosinophilia, thrombocytosis, leukopenia, elevated transaminases</td>
</tr>
<tr>
<td></td>
<td>levofloxacin 750 mg PO OD x 5 d</td>
<td>Combine with 3rd gen cephalosporin</td>
<td>See above</td>
</tr>
<tr>
<td></td>
<td>moxifloxacin 400 mg PO OD x 7 d (5 d for AECOPD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Piperacillin/ Tazobactam (Tazocin®) 4.5 g IV q6-8h x 7-10 d</td>
<td>Suspect Pseudomonas</td>
<td>CNS (confusion, convulsions, drowsiness), rash, Hematologic (abnormal platelet aggregation, prolonged PT, positive Coombs)</td>
</tr>
<tr>
<td></td>
<td>Vancomycin (Vancocin®) 1 g IV bid x 7-10 d</td>
<td>Suspect MRSA</td>
<td>CNS (chills, drug fever), hematologic (eosinophilia), rash, red man syndrome, interstitial nephritis, renal failure, ototoxicity</td>
</tr>
<tr>
<td></td>
<td>Macrolide azithromycin 500 mg IV OD x 2 d, then 500 mg PO OD x 5 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>clarithromycin 500 mg PO bid x 7-10 d</td>
<td>Suspect Legionella</td>
<td>See above</td>
</tr>
<tr>
<td><strong>ICU MEDICATIONS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressors/Inotropes norepinephrine (Levophed®) 0.5-30 µg/min IV</td>
<td>Acute hypotension</td>
<td>Angina, bradycardia, dyspnoea, hyper/hypotension, arrhythmias</td>
<td></td>
</tr>
<tr>
<td></td>
<td>phenylephrine 0.5 µg/kg/min IV</td>
<td>Severe hypotension</td>
<td>See above</td>
</tr>
<tr>
<td></td>
<td>dobutamine 2-20 µg/kg/min IV</td>
<td>Inotropic support</td>
<td>See above</td>
</tr>
<tr>
<td>Sedatives/Analgesia fentanyl (opioid class) 50-100 µg then 50-unlimited µg/h IV</td>
<td>Sedation and/or analgesia</td>
<td>Bradycardia, respiratory depression, drowsiness, hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>propofol (anesthetic) 1-3 mg/kg then 0.3-5 mg/kg/h IV</td>
<td>Sedation and/or analgesia</td>
<td>Apnea, bradycardia, hypotension (good for ventilator sedation)</td>
</tr>
</tbody>
</table>

See Infectious Diseases, ID27 – for the management of pulmonary tuberculosis.

### Landmark Respirology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS Network</td>
<td>NEJM 2000; 342:1301-8</td>
<td>Mortality decreased in ARDS patients ventilated with a low tidal volume strategy</td>
</tr>
<tr>
<td>Berlin Criteria</td>
<td>JAMA 2012; 307:2526-33</td>
<td>The new definition of ARDS, better predicts mortality</td>
</tr>
<tr>
<td>CPAP and Apnea</td>
<td>NEJM 2005; 353:2025-33</td>
<td>CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>NEJM 2012; 366:1287-97</td>
<td>Fixed dose of rivoxabarbin was non-inferior to standard therapy (Vit K antagonist) initial and long-term treatment of PE</td>
</tr>
<tr>
<td>Emphysema Treatment Trial</td>
<td>NEJM 2003; 348:2059-73</td>
<td>Lung volume reduction surgery benefits patients with upper lobe disease and low exercise capacity</td>
</tr>
<tr>
<td>IELCAP</td>
<td>NEJM 2006; 355:1763-71</td>
<td>High survival rate in patients with early stage lung cancer detected by low dose CT screening</td>
</tr>
<tr>
<td>Lung Health</td>
<td>JAMA 1994; 272:1497-505</td>
<td>Aggressive smoking intervention significantly decreases the age-related decline in FEV, in middle-aged smokers with mild airways obstruction</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NEJM 1978; 298:801-9</td>
<td>Interstitial lung disease subsets have different prognoses and response to treatment (e.g. desquamative but not usual interstitial pneumonia respond well to corticosteroids)</td>
</tr>
<tr>
<td>POET-COPD</td>
<td>NEJM 2011; 364:1093-103</td>
<td>Tiotropium decreases the number of moderate-to-severe exacerbations in comparison to salmeterol</td>
</tr>
<tr>
<td>ROFLUMILAST</td>
<td>Lancet 2009; 374:695-703</td>
<td>Leukotriene inhibitors improve FEV, when used as add-on therapy in COPD patients on tiotropium or salmeterol</td>
</tr>
<tr>
<td>TORCH</td>
<td>NEJM 2007; 356:775-89</td>
<td>Combination of inhaled steroids and long-acting β2-agonists improves COPD symptoms, reduces exacerbations, and shows a trend to lowers mortality</td>
</tr>
<tr>
<td>UPLIFT</td>
<td>NEJM 2008; 359:1543-54</td>
<td>Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect FEV, decline</td>
</tr>
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Fibromyalgia
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Acronyms

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<table>
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<th></th>
<th></th>
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<tbody>
<tr>
<td>Ab</td>
<td>antibody</td>
</tr>
<tr>
<td>Ag</td>
<td>antigen</td>
</tr>
<tr>
<td>ANA</td>
<td>antinuclear antibody</td>
</tr>
<tr>
<td>ANCA</td>
<td>antineutrophil cytoplasmic antibody</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>anti-Smith antibodies</td>
</tr>
<tr>
<td>APLA</td>
<td>antiphospholipid antibody syndrome</td>
</tr>
<tr>
<td>AS</td>
<td>ankylosing spondylitis</td>
</tr>
<tr>
<td>AVN</td>
<td>avascular necrosis</td>
</tr>
<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
</tr>
<tr>
<td>CBC</td>
<td>complete blood count</td>
</tr>
<tr>
<td>CCP</td>
<td>cyclic citrullinated peptide</td>
</tr>
<tr>
<td>CMC</td>
<td>carpometacarpal joint</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CPPD</td>
<td>calcium pyrophosphate dihydrate</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>DIP</td>
<td>distal interphalangeal joint</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>DMARD</td>
<td>disease-modifying anti-rheumatic drug</td>
</tr>
<tr>
<td>DMN</td>
<td>dermatomyositis</td>
</tr>
<tr>
<td>EA</td>
<td>enteropathic arthritis</td>
</tr>
<tr>
<td>ESR</td>
<td>erythrocyte sedimentation rate</td>
</tr>
<tr>
<td>GC</td>
<td>Neisseria gonorrhoeae/gonococcus</td>
</tr>
<tr>
<td>GCA</td>
<td>giant cell arteritis</td>
</tr>
<tr>
<td>GPA</td>
<td>granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>H/A</td>
<td>headache</td>
</tr>
<tr>
<td>Hb</td>
<td>hemoglobin</td>
</tr>
<tr>
<td>HLA</td>
<td>human leukocyte antigen</td>
</tr>
<tr>
<td>IA</td>
<td>intra-articular</td>
</tr>
<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>IE</td>
<td>infective endocarditis</td>
</tr>
<tr>
<td>MCP</td>
<td>metacarpal phalangeal joint</td>
</tr>
<tr>
<td>MCTD</td>
<td>mixed connective tissue disease</td>
</tr>
<tr>
<td>MHC</td>
<td>major histocompatibility complex</td>
</tr>
<tr>
<td>MPO</td>
<td>myeloperoxidase</td>
</tr>
<tr>
<td>MTP</td>
<td>metatarsal phalangeal joint</td>
</tr>
<tr>
<td>MTX</td>
<td>methotrexate</td>
</tr>
<tr>
<td>OA</td>
<td>osteoarthritis</td>
</tr>
<tr>
<td>PAN</td>
<td>polyarteritis nodosa</td>
</tr>
<tr>
<td>PIP</td>
<td>proximal interphalangeal joint</td>
</tr>
<tr>
<td>PM</td>
<td>polymyalgia</td>
</tr>
<tr>
<td>PMR</td>
<td>polymyalgia rheumatica</td>
</tr>
<tr>
<td>PTA</td>
<td>psoriatic arthritis</td>
</tr>
<tr>
<td>PTT</td>
<td>partial thromboplastin time</td>
</tr>
<tr>
<td>PUD</td>
<td>peptic ulcer disease</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RBC</td>
<td>red blood cell</td>
</tr>
<tr>
<td>ReA</td>
<td>reactive arthritis</td>
</tr>
<tr>
<td>RF</td>
<td>rheumatoid factor</td>
</tr>
<tr>
<td>RGM</td>
<td>range of motion</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SS</td>
<td>Sjögren’s syndrome</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td>UA</td>
<td>urinalysis</td>
</tr>
<tr>
<td>ULN</td>
<td>upper limit of normal</td>
</tr>
<tr>
<td>VDRL</td>
<td>venereal disease research laboratory</td>
</tr>
<tr>
<td>WBC</td>
<td>white blood cell</td>
</tr>
</tbody>
</table>
Anatomy of Joint Pathology

Figure 1. Structure of normal, degenerative, and inflammatory joint

Basics of Immunology

Immune Mechanisms of Disease

Table 1. Mechanisms of Immunologically Mediated Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathophysiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylactic (type I)</td>
<td>Formation of IgE → release of immunologic mediators from basophils/mast cells → diffuse inflammation</td>
<td>Asthma, Allergic rhinitis</td>
</tr>
<tr>
<td>Cytotoxic (type II)</td>
<td>Formation of Ab → deposit and bind to Ag on cell surface → phagocytosis or lysis of target cell</td>
<td>Autoimmune hemolytic anemia, Goodpasture’s syndrome, Graves’ disease, pernicious anemia</td>
</tr>
<tr>
<td>Immune complex (type III)</td>
<td>Formation of Ag-Ab complexes → activate complement → attract inflammatory cells and release cytokines</td>
<td>SLE, PAN, post-streptococcal glomerulonephritis, serum sickness</td>
</tr>
<tr>
<td>Cell-mediated/delayed hypersensitivity (type IV)</td>
<td>Release of cytokines by sensitized T-cells and T-cell mediated cytotoxicity</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>

Immunogenetics and Disease

- cell surface molecules called HLAs play a role in mediating immune reactions
- MHCs are genes on the short arm of chromosome 6 that encode HLA molecules
- there are three classes of MHCs
- discrete domains of hypervariability within MHC molecules thought to represent “susceptibility determinants”
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases

Table 2. Classes of MHCs

<table>
<thead>
<tr>
<th>MHC Class</th>
<th>Types</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>HLA-A, B, C</td>
<td>All cells</td>
<td>Recognized by CD8+ (cytotoxic) T-lymphocytes</td>
</tr>
<tr>
<td>II</td>
<td>HLA-DP, DQ, DR</td>
<td>Ag presenting cells (mononuclear phagocytes, B cells, etc.)</td>
<td>Recognized by CD4+ (helper) T-lymphocytes</td>
</tr>
<tr>
<td>III</td>
<td>Some components of the complement cascade</td>
<td>In plasma</td>
<td>Chemotaxis, opsonization, lysis of bacteria and cells</td>
</tr>
</tbody>
</table>

Terminology in Rheumatology

- Arthritis: joint swelling, effusion/synovial thickening, Decreased ROM, Stress pain (pain at the end of ROM), Increased warmth
- Arthralgia: perception of joint pain without obvious clinical findings
- Active joint: swollen joint, joint line tenderness, or stress pain

© Desmond Ballance 2006 (after Frances Yeung 2005)
### Table 3. HLA-Associated Rheumatic Disease

<table>
<thead>
<tr>
<th>HLA Type</th>
<th>Associated Conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27</td>
<td>AS, ReA, EA</td>
<td>In AS, relative risk = 70-90x; In ReA, relative risk = 40x</td>
</tr>
<tr>
<td>DR4, DR1</td>
<td>RA</td>
<td>In RA, relative risk = 2-10x; found in 93% of patients</td>
</tr>
<tr>
<td>DR3</td>
<td>SS, SLE</td>
<td>DR3 associated with many non-rheumatic conditions (celiac disease, type 1 DM, Graves’ disease, chronic active hepatitis)</td>
</tr>
</tbody>
</table>

### Differential Diagnoses of Common Presentations

#### Figure 2. Clinical approach to joint pain

- **Inflammatory**
  - Seropositive: RA, SLE, Scleroderma, DM/M/PM
  - Seronegative: SS, SLE

- **Crystal**: Gout, Pseudogout, Hydroxyapatite

- **Infectious/Septic**: Non-gonococcal

- **Degenerative**: OA, Tumor

- **Secondary**: Metabolic, Neuropathic, Trauma

- **Localized**: Bursitis, Tendinitis, Muscle sprain

- **Generalized**: PMR, Fibromyalgia

#### Table 4. Differential Diagnosis of Monoarthritis

<table>
<thead>
<tr>
<th>Infection</th>
<th>Crystal</th>
<th>Trauma</th>
<th>Neoplasic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic arthritis (Staph, GC, fungi, TB)</td>
<td>Gout, Pseudogout, Hydroxyapatite</td>
<td>OA</td>
<td>Hemarthrosis, Osteonecrosis, Tumor</td>
<td>Systemic inflammatory disease, Polyarthritis presenting with monarticular symptoms first</td>
</tr>
</tbody>
</table>

#### Table 5. Differential Diagnosis of Oligoarthritis/Polyarthritis

<table>
<thead>
<tr>
<th>Acute (&lt;6 weeks)</th>
<th>Chronic (&gt;6 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First presentation of inflammatory arthritis</strong></td>
<td><strong>Seropositive inflammatory arthritis</strong></td>
</tr>
<tr>
<td>Post-viral (panovirus B19)</td>
<td>RA, SLE</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Infectious (GC, non-GC)</td>
<td>DM/M/PM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Seronegative inflammatory arthritis</strong></th>
<th><strong>Degenerative OA</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>AS</td>
<td>OA</td>
</tr>
<tr>
<td>EA</td>
<td>PsA</td>
</tr>
<tr>
<td>ReA</td>
<td>Crystal (polarticular gout)</td>
</tr>
</tbody>
</table>

#### Table 6. Symptoms of Inflammatory Arthritis vs. Degenerative Arthritis

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Degenerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at rest, relieved by motion</td>
<td>Pain with motion, relieved by rest</td>
</tr>
<tr>
<td>Morning stiffness &gt; 1 h</td>
<td>Morning stiffness &lt; 1/2 h</td>
</tr>
<tr>
<td>Warmth, swelling, erythema</td>
<td>Joint instability, buckling, locking</td>
</tr>
<tr>
<td>Malalignment, deformity</td>
<td>Bony enlargement, malalignment, deformity</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td>Extra-articular manifestations</td>
</tr>
</tbody>
</table>

**Causes of Joint Pain**
- SOFTER TISSUE
  - Sepsis
  - OA
  - Fracture
  - Tendon/muscle
  - Epiphyseal
  - Referred
  - Tumor
  - Ischemia
  - Seropositive arthritides
  - Seronegative arthritides
  - Urate (gout)/other crystal
  - Extra-articular rheumatism (PMR/fibromyalgia)

**Patterns of Joint Involvement**
- Symmetrical vs. asymmetrical
- Small vs. large
- Mono vs. oligo (2-4 joints) vs. polyarticular (>5 joints)
- Axial vs. peripheral
Table 7. Seropositive vs. Seronegative Rheumatic Diseases

<table>
<thead>
<tr>
<th></th>
<th>Seropositive</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td>F&gt;M</td>
<td>M&gt;F</td>
</tr>
<tr>
<td><strong>Peripheral Arthritis</strong></td>
<td>Symmetrical</td>
<td>Usually asymmetrical</td>
</tr>
<tr>
<td></td>
<td>Small (PIP, MCP) and medium joints (wrist, knee, ankle, elbow) common DIP less involved</td>
<td>Usually larger joints, lower extremities (PsA may be the exception)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dactylitis (“sausage digit”)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enthesitis</td>
</tr>
<tr>
<td><strong>Pelvic/Axial Disease</strong></td>
<td>No (except for C-spine)</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Enthesitis</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Extra-Articular</strong></td>
<td>Nodules</td>
<td>Iritis (anterior uveitis)</td>
</tr>
<tr>
<td></td>
<td>Vasculitis</td>
<td>Oral ulcers</td>
</tr>
<tr>
<td></td>
<td>Sicca</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td></td>
<td>Raynaud’s phenomenon</td>
<td>Dermatologic features</td>
</tr>
</tbody>
</table>

Common Investigations in Rheumatology

- general: CBC, electrolytes, Cr
- acute phase reactants: ESR, CRP, ferritin, albumin, fibrinogen, platelets
- complement (C3, C4)
- U/A to detect disease complications (proteinuria, active sediment)
- serology: autoimmune Abs (ANA, anti-dsDNA, anti-Jo-1, anti-Sm, anti-La, anti-Ro, RF, and anti-CCP)
- synovial fluid analysis
- radiology (plain film, CT, MRI, U/S, bone densitometry, angiography, bone scan)

**Synovial Fluid Analysis**

- synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage

**Indications**

- diagnostic: mandatory if septic arthritis suspected; advised if crystal arthritis or hemarthrosis suspected; advised if unexplained effusion in accessible joint
- therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection

**Contraindications**

- absolute: open lesion or suspected infection of overlying skin or soft tissue
- relative: bleeding diathesis, thrombocytopenia, prosthetic joint

**Most Important Tests of Synovial Fluid (3 Cs)**

- ensure synovial fluid is described in terms of color, clarity, viscosity, and quantity

1. Cell count and differential
2. Culture and Gram stain (bacteria, mycobacteria, fungi)
3. Crystal examination (microscopy with polarized light)
   - gout (monosodium urate) → needle-shaped, negatively birefringent (bright yellow)
   - pseudogout (calcium pyrophosphate dihydrate) → rhomboid-shaped, positively birefringent (pale blue)

**Table 8. Synovial Fluid Analysis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Non-Inflammatory</th>
<th>Inflammatory</th>
<th>Infectious</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Color</strong></td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Yellow to white</td>
<td>Red/brown</td>
</tr>
<tr>
<td><strong>Clarity</strong></td>
<td>Clear</td>
<td>Clear</td>
<td>Opaque</td>
<td>Opaque</td>
<td>Sanguineous</td>
</tr>
<tr>
<td><strong>Viscosity</strong></td>
<td>High (due to hyaluronic acid)</td>
<td>High</td>
<td>Low</td>
<td>Low or paradoxically high if purulent</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>WBC/mm³</strong></td>
<td>&lt;200</td>
<td>&lt;2000</td>
<td>&gt;2000</td>
<td>Higher cell counts (particularly &gt;50,000) suggestive</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>% PMN</strong></td>
<td>&lt;25%</td>
<td>&lt;25%</td>
<td>&gt;25%</td>
<td>&gt;75%</td>
<td>Variable</td>
</tr>
<tr>
<td><strong>Culture/ Gram Stain</strong></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Usually positive</td>
<td>–</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>Trauma</td>
<td>Seropositive</td>
<td>S. aureus</td>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OA</td>
<td>Seronegatives</td>
<td>Gram negative</td>
<td>Hemophilia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td>Crystal</td>
<td>GC → difficult to culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertrophic – arthropathy</td>
<td>Arthropathies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Septic Arthritis

• for any acute monoarticular arthritis, one must rule out septic etiology; consider empiric antibiotic treatment until septic arthritis is excluded by history, physical exam, and synovial fluid analysis
• poor prognostic factors: older age, immunocompromised, delay in treatment, previously damaged joint, joint prosthesis
• see Infectious Diseases for Gonococcal Arthritis, ID15/Orthopedics, OR10

Degenerative Arthritis: Osteoarthritis

Definition
• progressive deterioration of cartilage and bone due to failed repair of joint damage caused by stresses on the joint

Classification (Based on Etiology)
• primary (idiopathic)
  ▪ most common, unknown etiology
• secondary
  ▪ post-traumatic or mechanical
  ▪ post-inflammatory (e.g. RA) or post-infectious
  ▪ heritable skeletal disorders (e.g. scoliosis)
  ▪ endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
  ▪ metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson's disease, ochronosis)
  ▪ neuropathic (e.g. Charcot joints)
    ▪ atypical joint trauma due to peripheral neuropathy (e.g. DM, syphilis)
  ▪ AVN
  ▪ other (e.g. congenital malformation)

Pathophysiology
• deterioration of articular cartilage due to local biomechanical factors, which leads to joint trauma and release of proteolytic and collagenolytic enzymes
  ▪ OA develops when cartilage catabolism > synthesis
  ▪ loss of proteoglycans and water exposes underlying bone
• abnormal local bone metabolism further damages joint
• altered joint function and damage
• synovitis is secondary to cartilage damage; therefore, may see small effusions in OA

Epidemiology
• most common arthropathy
• increased prevalence with increasing age (35% of 30 yr olds, 85% of 80 yr olds)

Risk Factors
• genetic predisposition, advanced age, obesity (for knee OA), female, trauma

Signs and Symptoms
• localized to affected joints (not a systemic disease)
• pain is often insidious, gradually progressive, with intermittent flares and remissions

Table 9. Signs and Symptoms of OA

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint line tenderness; stress pain ± joint effusion</td>
<td>Joint pain with motion; relieved with rest</td>
</tr>
<tr>
<td>Bony enlargement at affected joints</td>
<td>Short duration of stiffness (&lt;1/2 h) after immobility</td>
</tr>
<tr>
<td>Malalignment/deformity (angulation)</td>
<td>Joint instability/buckling</td>
</tr>
<tr>
<td>Limited ROM</td>
<td>Joint locking due to “joint mouse” (bone or cartilage fragment)</td>
</tr>
<tr>
<td>Crepitus on passive ROM</td>
<td>Loss of function or other internal derangements (e.g. meniscal tear)</td>
</tr>
<tr>
<td>Inflammation (mild if present)</td>
<td></td>
</tr>
<tr>
<td>Periarticular muscle atrophy</td>
<td></td>
</tr>
</tbody>
</table>

Joint Involvement
• asymmetric
• hand
  ▪ DIP (Heberden’s nodes = osteophytes → enlargement of joints)
  ▪ PIP (Bouchard’s nodes)
  ▪ CMC (usually thumb squaring)
  ▪ 1st MCP (other MCPs are usually spared)
• hip
  - usually presents as groin pain ± dull or sharp pain in the trochanteric area, internal rotation and abduction are lost first
  - pain can radiate to the anterior thigh, but generally does not go below the knee
• knee
  - initial narrowing of one compartment, medial > lateral; seen on standing x-rays, often patellar-femoral joint involved
• foot
  - common in first MTP and midfoot
• lumbar spine
  - very common, especially L4-L5, L5-S1
  - degeneration of intervertebral discs and facet joints
  - reactive bone growth can contribute to neurological impingement (e.g. sciatica, neurogenic claudication) or spondylolisthesis (forward or backward movement of one vertebra over another)
• cervical spine
  - commonly presents with neck pain that radiates to scapula, especially in mid-lower cervical area (C5 and C6)

Investigations
• blood work
  - normal CBC and ESR, CRP
  - negative RF and ANA
• radiology: 4 hallmark findings
• synovial fluid: non-inflammatory (see Table 8)

Treatment
• presently no treatment alters the natural history of OA
• non-pharmacological therapy
  - weight loss (minimum 5-10 lb loss) if overweight
  - physiotherapy: heat/cold, low impact exercise programs
  - occupational therapy: aids, splints, cane, walker, bracing
• pharmacological therapy (see Table 32)
  - oral: acetaminophen/NSAIDs, glucosamine ± chondroitin (nutraceuticals not proven)
  - joint injections: corticosteroid, hyaluronic acid (questionable benefit)
  - topical: capsaicin, NSAIDs
• surgical treatment
  - joint debridement, osteotomy, total and/or partial joint replacement, fusion
  (see Orthopedics, OR28)

SEROPOSITIVE RHEUMATIC DISEASE
• diagnosis vs. classification in rheumatology
  - diagnostic criteria are often dependent on disease progression and evolution over time, as early objective measures are often unavailable
  - classification criteria are derived from studying patients with long-term diseases and clear diagnoses in order to determine which criteria have good specificity in the early prediction of certain diagnoses
• seropositive arthropathies are characterized by the presence of a serologic marker such as positive RF or ANA
• a small subset of the vasculitides, the small vessel ANCA-associated vasculitides, have a measurable serological component, but even these are often considered a separate entity from seropositive disease by experts

Blood Work
• general: CBC, Cr
• acute phase reactants: ESR, CRP, ferritin, albumin, complement (C3 and C4), fibrinogen
• note: C3, C4 often decrease in active SLE
• autoantibodies

Urinalysis
• proteinuria, active sediment

Synovial Fluid Analysis
• see Table 8

Radiology
• plain film, CT, MRI, US, bone densitometry, angiography, and bone scan
### Table 10. Autoantibodies and their Prevalence in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Disease</th>
<th>Healthy Controls</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>RA 80%</td>
<td>&lt;5%</td>
<td>Autoantibodies (IgM&gt;IgG&gt;IgA) directed against Fc domain of IgG. Present in most seropositive diseases. Levels correlate with disease severity in RA. Non-specific. Present in IE, TB, hepatitis C, silicosis, sarcoidosis.</td>
</tr>
<tr>
<td></td>
<td>SS 50%</td>
<td>10-20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SLE 20%</td>
<td>&gt;65</td>
<td></td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>RA 80%</td>
<td></td>
<td>In RA: anti-CCP more specific than RF. May be useful in early disease and to predict aggressive disease.</td>
</tr>
<tr>
<td>ANA</td>
<td>SLE 98%</td>
<td>&lt;5% (seen in other CTDs)</td>
<td>Ab against nuclear components (DNA, RNA, histones, centromere). Sensitive but not specific for SLE.</td>
</tr>
<tr>
<td></td>
<td>MCTD 95%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SS 70-90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CREST 80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>SLE 50-70%</td>
<td>0%</td>
<td>Specific for SLE. Levels correlate with disease activity.</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>SLE &lt;30%</td>
<td>0%</td>
<td>Specific but not sensitive for SLE.</td>
</tr>
<tr>
<td>Anti-Ro (SSA)</td>
<td>SS 40-95%</td>
<td>0.5%</td>
<td>Subacute cutaneous SLE and mothers of babies with neonatal SLE 25%.</td>
</tr>
<tr>
<td>Anti-La (SSB)</td>
<td>SS 40%</td>
<td>0%</td>
<td>Usually occurs with anti-Ro.</td>
</tr>
<tr>
<td>Anti-phospholipid Ab (LAC, ACLA)</td>
<td>APLA 100%</td>
<td>&lt;5%</td>
<td>By definition present in APLA. Only small subset of APLA patients develop clinical syndrome of APLA. If positive, will often get a false positive VDRL test.</td>
</tr>
<tr>
<td></td>
<td>SLE 31-40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Histone</td>
<td>Drug-induced SLE &gt;90%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Idiopathic SLE &gt;50%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>MCTD</td>
<td>Present in MCTD; present in many other CTDs.</td>
<td></td>
</tr>
<tr>
<td>Anti-Centromere</td>
<td>CREST &gt;80%</td>
<td>0%</td>
<td>Specific for CREST variant of systemic sclerosis.</td>
</tr>
<tr>
<td>Anti-Topoisomerase I (formerly Scl-70)</td>
<td>Diffuse systemic sclerosis 26-76%</td>
<td>0%</td>
<td>Specific and sensitive</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>Active GPA (Wegener’s) &gt;90%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>p-ANCA</td>
<td>GPA (Wegener’s) 10% Other vasculitis</td>
<td>0%</td>
<td>Nonspecific and poor sensitivity (found in ulcerative colitis, PAN, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis).</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>DMM 15-20%</td>
<td></td>
<td>Specific but not sensitive (not available in all centers).</td>
</tr>
<tr>
<td>Ab Against RBCs, WBCs, or Platelets</td>
<td>SLE</td>
<td>Perform direct Coomb’s test. Test Hb, reticulocyte, leukocyte and platelet count, antiplatelet Abs.</td>
<td></td>
</tr>
</tbody>
</table>

• note: some individuals in the normal population test positive for RF and/or ANA, but do not have the conditions listed in Table 10
## Connective Tissue Disorders

### Table 11. Features of Seropositive Arthropathies

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>SLE</th>
<th>Scleroderma</th>
<th>Dermatomyositis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Symmetrical polyarthritis (small joint involvement)</td>
<td>Multisystemic disease: rash, photosensitivity, Raynaud’s, arthalgia, cardiac and pulmonary serositis, CNS symptoms, glomerulonephritis</td>
<td>Skin tightness, stiffness of fingers, Raynaud’s, heartburn, dysphagia, pulmonary HTN, renal crisis with new onset HTN or hypertensive urgency/emergency, dyspnea on exertion</td>
<td>Heliotrope rash (periarticular), Gottron’s papules (violaceous papules over knuckles and IP joints)</td>
</tr>
<tr>
<td><strong>Physical Examination</strong></td>
<td>Effused joints Nodules Joint deformities Bone-on-bone crepitus in advanced disease</td>
<td>Confirm historical findings (rash, serositis, renal, CVS, etc.) ± effused (typically small) joints (can be minimal, look for soft tissue swelling)</td>
<td>Skin tightness on dorsum of hand, facial skin tightening, telangectasia, calcinosis, non-eroded joint, inspiratory crackles</td>
<td>Rash, proximal muscle weakness, inspiratory crackles</td>
</tr>
<tr>
<td><strong>LABORATORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-Specific</strong></td>
<td>↑ ESR in 50-80%</td>
<td>↑ platelets</td>
<td>Normal WBC</td>
<td>Possible increased ESR</td>
</tr>
<tr>
<td></td>
<td>↓ WBC (Felty’s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specific</strong></td>
<td>RF +ve in ~80%</td>
<td>Anti-CCP +ve in ~80%</td>
<td>ANA +ve in &gt;90%</td>
<td>CK elevated in 80%</td>
</tr>
<tr>
<td></td>
<td>Anti-diSS DNA +ve in 50-70%</td>
<td></td>
<td>Anti-topoisomerase 1 (diffuse)</td>
<td>ANA +ve in &gt;90%</td>
</tr>
<tr>
<td></td>
<td>Anti-SM +ve in 30%</td>
<td>Total hemolytic complement</td>
<td>Anti-centromere (usually in CREST, see RH13)</td>
<td>Anti-topoisomerase 1 (diffuse)</td>
</tr>
<tr>
<td></td>
<td>False positive VDRL (in SLE subtypes)</td>
<td>↑ PTT (in SLE subtypes, e.g. APLA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Synovial Fluid</strong></td>
<td>Inflammation</td>
<td>Mild inflammation with ↑ ve ANA</td>
<td>Not specific</td>
<td>Not specific</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis (&gt;10,000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Radiographs</strong></td>
<td>Periarticular osteopenia</td>
<td>Non-erosive</td>
<td>± pulmonary fibrosis</td>
<td>± esophageal dysmotility</td>
</tr>
<tr>
<td></td>
<td>Joint space narrowing</td>
<td>± osteopenia</td>
<td>± esophageal dysmotility</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erosions</td>
<td>± soft tissue swelling</td>
<td>± calcinosis</td>
<td>± interstitial lung disease</td>
</tr>
<tr>
<td></td>
<td>Absence of bone repair</td>
<td>Symmetric/concentric</td>
<td>± interstitial lung disease</td>
<td>± calcifications</td>
</tr>
</tbody>
</table>

### Rheumatoid Arthritis

**Definition**
- chronic, symmetric, erosive synovitis of peripheral joints (e.g. wrists, MCPs, MTPs)
- characterized by a number of extra-articular features

**Table 12. Classification Criteria for RA**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Joint involvement (swollen or tender)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 large joint (shoulders, elbows, hips, knees, and ankles)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4-10 small joints</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>2. Serology</td>
<td></td>
<td>Total score of ≥8: definite RA Must have ≥1 joint with definite clinical swelling, not better explained by other disease</td>
</tr>
<tr>
<td>Negative RF and negative Anti-CCP</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low-positive RF or low-positive Anti-CCP (&lt;3 x ULN)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>High-positive RF or high-positive Anti-CCP (&gt;3 x ULN)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3. Acute phase reactants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abnormal CRP and abnormal ESR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4. Duration of symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 wk</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥6 wk</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Arthritis Rheum 2010;62:2569-2581

RA is an independent risk factor for atherosclerosis and CV disease; RA is associated with increased overall mortality/morbidity from all causes: CV disease, neoplasm (especially lymphoma), infection

**Common Presentation**
- Morning stiffness >1 h, improves with use
- Symmetric joint involvement
- Initially involves small joints of hands and feet
- Constitutional symptoms

**1987 American Rheumatism Association RA Criteria**
At least 4 of:
- Morning stiffness >1 h for >6 wk
- Arthritis ≥3 joints for >6 wk
- Arthritis of hand joints for >6 wk
- Arthritis of foot joints for >6 wk
- Symmetric arthritis for >6 wk
- Rheumatoid nodules
- Serum RF positive
- Radiographic changes (erosions or periarticular osteoporosis)

Criteria are 91-94% sensitive and 89% specific for RA
**Pathophysiology**
- autoimmune disorder, unknown etiology
- hallmark of RA is hypertrophy of the synovial membrane
  - activated rheumatoid synovium (pannus) grows into and over the articular surface; inflammatory mediators lead to release of metalloproteinases and collagens resulting in destruction of articular cartilage and subchondral bone
- two theories attempt to explain chronic remissions and exacerbations seen in RA
  - **sequestered Ag**
    - during inflammation, immune complexes (ICs) are deposited at avascular cartilage-bone junction → immune complexes are released as further cartilage breaks down → triggers inflammatory cascade
  - **molecular mimicry**
    - cartilage damage → altered cartilage resembles undefined offending agent → triggers inflammatory cascade

**Epidemiology**
- prevalence 1% of adult population
- F:M = 3:1
- age of onset 20-40 yr
- genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type)

**Signs and Symptoms**
- variable course of exacerbations and remissions
- morning stiffness >1 h, improves with use, increases with rest
- may have joint pain with activity
- symmetric joint involvement
- joint swelling, tender joints
- constitutional symptoms: profound fatigue; rarely myalgia or weight loss
- extra-articular features (EAF)
- complications of chronic synovitis
  - signs of mechanical joint damage: loss of motion, instability, deformity, crepitus, joint deformities
    - swan neck deformity, boutonnière deformity
    - ulnar deviation of MCP, radial deviation of wrist joint
    - hammer toe, mallet toe, claw toe
    - flexion contractures
  - atlanto-axial and subaxial subluxation
  - C-spine instability
  - neurological impingement (long tract signs)
  - difficult/dangerous intubation: risk of worsening subluxation and damage to spinal cord
- limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
- carpal tunnel syndrome
- ruptured Baker's cyst (outpouching of synovium behind the knee); presentation similar to acute DVT

<table>
<thead>
<tr>
<th>Table 13. Extra-Articular Features of RA Classified by Underlying Pathophysiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>System</td>
</tr>
<tr>
<td>Skin</td>
</tr>
<tr>
<td>Ocular</td>
</tr>
<tr>
<td>Head and Neck</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Pulmonary</td>
</tr>
<tr>
<td>Neurologic</td>
</tr>
<tr>
<td>Hematologic</td>
</tr>
<tr>
<td>Renal</td>
</tr>
</tbody>
</table>

**Classification of Global Functional Status in RA**
- **Class I**: able to perform usual ADLs (self-care, vocational, avocational)
- **Class II**: able to perform self-care and vocational activities, restriction of avocational activities
- **Class III**: able to perform self-care, restriction of vocational and avocational activities
- **Class IV**: limited ability to perform self-care, vocational, and avocational activities

**Syndromes in RA**
- SS (common): keratoconjunctivitis sicca and xerostomia (dry eyes and mouth)
- Caplan’s syndrome (rare): multiple pulmonary nodules and pneumoconiosis
- Felty’s syndrome (rare): arthritis, splenomegaly, neutropenia
Investigations

- blood work
  - RF sensitivity ~80% but non-specific; may not be present at onset of symptoms
  - anti-CCP: sensitivity ~80% but more specific; may precede onset of symptoms
  - increased disease activity associated with decreased Hb (anemia of chronic disease), increased platelets, ESR, CRP, and RF

- imaging
  - x-rays may be entirely normal at onset
  - first change is periarticular osteopenia, followed by erosions
  - U/S, MRI may be used to image hands to detect early synovitis and erosions

Treatment

- goals of therapy: remission or lowest possible disease activity
  - control disease activity
  - relieve pain and stiffness
  - maintain function and lifestyle
  - prevent or control joint damage
  - key is early diagnosis and early intervention with DMARDs
  - “window of opportunity” = early treatment within first 3 mo of disease may allow better control/remission

Education

- The Arthritis Society (Canada), Arthritis Foundation (U.S.), The Rheumatoid Patient Foundation for educational resources

Behavioral

- exercise program (isometrics and active, gentle ROM exercise during flares, aquatic/aerobic/strengthening exercise between flares), assistive devices as needed
- job modification may be necessary

Pharmacologic

1. DMARDs and Biologics (see Table 33)
   - DMARDs: standard of care and should be started as soon as possible
   - treatments guided by disease severity and prognostic features
   - MTX is the gold standard and is first-line unless contraindicated
   - potential toxicities: GI, hematologic, hepatic (liver enzymes), pulmonary, teratogenic
   - if inadequate response (3-6 mo) → combine or switch
   - add-ons include: hydroxychloroquine, sulfasalazine, leflunomide
   - biologics: indicated if inadequate response to DMARDs
     - can be combined with DMARD therapy
     - agents include infliximab, etanercept, adalimumab, abatacept, rituximab, tocilizumab
     - reassess every 3-6 mo and monitor disease severity

2. Reducing Inflammation and Pain
   - NSAIDs
     - individualize according to efficacy and tolerability
     - contraindicated or cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy); add acetaminophen ± opioid prn for synergistic pain control
   - corticosteroids
     - local
       - IA injections to control symptoms in a specific joint
       - systemic (prednisone)
         - low dose (5-10 mg/d) useful for short-term to improve symptoms if NSAIDs ineffective, to bridge gap until DMARD takes effect
         - for severe RA, low dose prednisone can be added to DMARDs
         - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy if using corticosteroids >3 mo at >7.5 mg/d
     - cautions/contraindications: active infection, TB, osteoporosis, HTN, gastric ulcer, DM

Follow-Up Management of Established RA

- follow-up every 3-6 mo, then 6-12 mo after inflammation has been suppressed
- examine joints for active inflammation – if active, consider adjusting medications, referral to specialist, PT/OT
- if assessment reveals joint damage – consider analgesia, referral to PT/OT, surgical options

Surgical Therapy

- indicated for structural joint damage
- surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair

Diagnosis Criteria of SLE

MD SOAP BRAIN
- Malar rash
- Discoid rash
- Oral ulcers
- A/N/A
- Photosensitivity

Side Effects of Steroids

- Weight gain
- Osteoporosis
- AVN
- Cataracts, glaucoma
- PUD
- Susceptibility to infection
- Easy bruising
- Acne
- HTN
- Hyperlipidemia
- Hypokalemia, hyperglycemia
- Mood swings

Comparison of Treatment Strategies in Early Rheumatoid Arthritis

Study: RCT of 508 patients comparing 4 different treatment strategies for early RA (known as the BEST trial).

Intervention:
  - Group 1: Sequential Monotherapy with traditional DMARDs
  - Group 2: Step-Up Combination Therapy
  - Group 3: Initial Combination Therapy with prednisone (high dose)
  - Group 4: Initial Combination Therapy with infliximab

Results: Patients in groups 3 and 4 responded faster and had significantly greater overall change in physical function scores after the first year of treatment. By end of the second year, groups 1 and 2 had achieved a similar response to groups 3 and 4. Groups 3 and 4 also showed significantly less radiologic progression of their disease over 2 yr than groups 1 and 2. There were no significant differences in toxicity levels between the 4 groups.

Conclusion: Initial combination therapy with prednisone or infliximab results in faster response rates. Whether faster initial response rates leads to better long-term disease outcomes has not yet been studied.
Systemic Lupus Erythematosus

- see Nephrology, NP24 and Dermatology, D38 for additional details

Definition
• chronic inflammatory multi-system disease of unknown etiology
• characterized by production of autoantibodies and diverse clinical manifestations

Table 14. Diagnostic Criteria of SLE*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>Classic “butterfly rash”, sparing of nasolabial folds, no scarring</td>
</tr>
<tr>
<td>Discoid rash</td>
<td>May cause scarring due to invasion of basement membrane</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash in reaction to sunlight</td>
</tr>
<tr>
<td>Oral/nasal ulcers</td>
<td>Usually painless</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Symmetric, involving ≥2 small or large peripheral joints, non-erosive</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleuritis or pericarditis</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>Seizures or psychosis</td>
</tr>
<tr>
<td>LABORATORY</td>
<td></td>
</tr>
<tr>
<td>Renal disorder</td>
<td>Proteinuria (≥0.5 g/d or 3+) Cellular casts (RBC, Hb, granular, tubular, mixed)</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia</td>
</tr>
<tr>
<td>Immunologic disorder</td>
<td>Anti-dsDNA or anti-Sm or antiphospholipid Ab (anticardiolipin Ab, SLE anticoagulant) or false positive VDRL with 6 mo confirmatory negative</td>
</tr>
<tr>
<td>ANA</td>
<td>Most sensitive test (98%), not specific</td>
</tr>
</tbody>
</table>

*Note: “4, 7, 11” rule = 4 (or more) out of 11 criteria (4 lab, 7 clinical) must be present, serially or simultaneously, for diagnosis

Etiology and Pathophysiology
• production of autoantibodies causing multi-organ inflammation
• multi-factorial etiology
• genetics
  ▪ common association with HLA-B8/DR3; ~10% have positive family history
  ▪ estrogen
    ▪ pre-pubertal and post-menopausal women have similar incidence to men
    ▪ men with SLE have higher concentration of estrogenic metabolites
• infection
  ▪ viral (non-specific stimulant of immune response)
  ▪ drug-induced
    ▪ anti-hypertensives (hydralazine), anti-convulsants (phenytoin), anti-arrhythmics (propranolol), isoniazid, biologics, oral contraceptive pills
  ▪ anti-histone Ab are commonly seen in drug-induced SLE
• symptoms resolve with discontinuation of offending drug

Epidemiology
• prevalence: 0.05% overall
• F:M = 10:1
• age of onset in reproductive yr (13-40)
• more common and severe in African Americans and Asians
• bimodal mortality pattern
  ▪ early (within 2 yr)
    ▪ active SLE, active nephritis, infection secondary to steroid use
  ▪ late (>10 yr)
    ▪ inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation

Signs and Symptoms
• characterized by periods of exacerbation and remission

The Safety of Infliximab, Combined with Background Treatments, among Patients with Rheumatoid Arthritis and Various Comorbidities (START)
Arthritis Rheum. 2008;54:1075-1086
Study: Multicenter RCT.
Patients: 1,084 patients (mean age 52 yr, 80% female) with active moderate to severe RA despite treatment with MTX.
Intervention: Patients were randomized to receive infusions of placebo, infliximab dosed at 3 mg/kg, or infliximab dosed at 10 mg/kg at 0, 2, 6, and 14 wk, in addition to MTX.
Primary Outcome: Incidence of serious infection within 22 wk.
Results: Compared with the placebo group, the relative risk of developing serious infection at 3 mg/kg and 10 mg/kg of infliximab was 1.0 (95% CI 0.3-3.3, p=0.999) and 3.1 (95% CI 1.2-7.9, p=0.013) respectively. In addition, 31% of patients receiving infliximab at 3 mg/kg and 32% of patients receiving infliximab at 10 mg/kg were able to achieve remission at 22 wk compared with only 14% of those receiving placebo (p<0.001, NNT=6).
Conclusions: Therapy with infliximab 3 mg/kg does not significantly increase the risk of serious infection in patients with active moderate to severe RA already receiving MTX. However, therapy with infliximab 10 mg/kg does significantly increase the risk of serious infection in this population.

ACR 2012 Update for the Use of DMARDs in the Treatment of RA
Arthritis Care & Research 2012;64(5):625-639
Indications for initiating and switching DMARDs and biologic agents:
• In patients with early RA (<6 mo), DMARD monotherapy is recommended in the absence of poor prognostic features, DMARD combination therapy is recommended for moderate/high disease activity and poor prognostic factors, anti-TNF biologic ± MTX is recommended for high disease activity and poor prognostic factors.
• In patients with established RA (>6 mo):
  ▪ If disease activity persists for 3 mo, move from monotherapy to DMARD polytherapy.
  ▪ If disease activity remains high after 2 mo of MTX monotherapy or DMARD combination therapy, add or switch to anti-TNF biologic, abatacept, or rituximab.
  ▪ If disease activity persists for 3 mo on anti-TNF biologic, switch to another anti-TNF biologic or non-TNF biologic.
• In patients with hepatitis C, etanercept could be potentially used; biologic agents are not recommended for untreated chronic hepatitis B patients.
• Biologic agents may be used in patients treated for solid malignancies or nonmelanoma skin cancer >5 yr ago.
• Anti-TNF agents should not be used in CHF patients with NYHA III or IV.
• Patients considered for biologic agents should be screened for latent TB infection.
• Vaccinations (pneumococcal, influenza, hepatitis B, HPV, and live attenuated VZV) should be administered prior to starting therapy with DMARDs or biologic agents.
Table 15. Symptoms of SLE

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Fatigue, malaise, weight loss, fever, lymphadenopathy</td>
</tr>
<tr>
<td>Renal</td>
<td>HTN, peripheral edema, glomerulonephritis, renal failure</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura, panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Polyarthralgias, polyarthritis, myalgias, AVN; reducible deformities of hand = Jaccoud's arthritis</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Keratoconjunctivitis sicca, episcleritis, scleritis, cytoid bodies (cotton wool exudates on fundoscopy = infarction of nerve cell layer of retina)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Pericarditis, CAD, non-bacterial endocarditis (Libman-Sachs) Note: SLE is an independent risk factor for atherosclerosis and CAD</td>
</tr>
<tr>
<td>Vascular</td>
<td>Raynaud’s phenomenon, livedo reticularis (mottled discoloration of skin due to narrowing of blood vessels, characteristic lacy or net-like appearance), thrombosis, vasculitis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pleuritis, interstitial lung disease, pulmonary HTN, PE, alveolar hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Pancreatitis, SLE enteropathy, hepatitis, hepatomegaly</td>
</tr>
<tr>
<td>Neurologic</td>
<td>H/A, depression, psychosis, seizures, cerebritis, transverse myelitis, peripheral neuropathy, stroke</td>
</tr>
</tbody>
</table>

Investigations

- blood work: ANA (sensitivity 98%, but poor specificity → used as a screening test, ANA titres are not useful to follow disease course)
- anti-dsDNA and anti-Sm are specific (95-99%)
- anti-dsDNA titer and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant
  - anti-dsDNA increases and C3 and C4 decrease with disease activity
- antiphospholipid Ab (anti-cardiolipin Ab and SLE anticoagulant), may cause increased risk of clotting and increased aPTT

Treatment

- goals of therapy
  - treat early and avoid long-term steroid use, if unavoidable see Endocrinology, E42 for osteoporosis management
  - if high doses of steroids necessary for long-term control, add steroid-sparing agents and taper when possible
  - treatment is tailored to organ system involved and severity of disease
  - all medications used to treat SLE require periodic monitoring for potential toxicity

- dermatologic
  - sunscreen, avoid UV light and estrogens
  - topical steroids, hydroxychloroquine

- musculoskeletal
  - NSAIDs → gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
  - hydroxychloroquine improves long-term control and prevents flares
  - bisphosphonates, calcium, vitamin D to combat osteoporosis

- organ-threatening disease
  - high-dose oral prednisone or IV methylprednisolone in severe disease
  - steroid-sparing agents: azathioprine, MTX, mycophenolate
  - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or SLE nephritis)

Antiphospholipid Antibody Syndrome

Definition

- multi-system vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions, and thrombocytopenia
- often presents with migraine-type headaches
- circulating antiphospholipid autoantibodies interfere with coagulation cascade

- primary APLA: occurs in the absence of other disease
- secondary APLA: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- catastrophic APLA: development within 1 wk of small vessel thrombotic occlusion in ≥3 organ systems with positive antiphospholipid Ab (high mortality)
Table 16. Classification Criteria of APLA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td>Vascular thrombosis Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia</td>
</tr>
<tr>
<td></td>
<td>Venous: DVT, PE, renal and retinal vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Must be confirmed by imaging or histopathology</td>
</tr>
<tr>
<td></td>
<td>Pregnancy morbidity Fetal death (&gt;10 wk GA), recurrent spontaneous abortions (&lt;10 wk GA) or premature birth (&lt;34 wk GA)</td>
</tr>
<tr>
<td>LABORATORY</td>
<td>Labs must be positive on 2 occasions, at least 12 wk apart</td>
</tr>
<tr>
<td>SLE</td>
<td>SLE anticoagulant</td>
</tr>
<tr>
<td></td>
<td>Anti-cardiolipin Ab IgG and/or IgM</td>
</tr>
<tr>
<td></td>
<td>Anti-β2-glycoprotein-I Ab IgG and/or IgM</td>
</tr>
</tbody>
</table>

*1 clinical and 1 laboratory criteria must be present for diagnosis


Signs and Symptoms
- see clinical criteria in Table 16
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud’s phenomenon, purpura, leg ulcers, and gangrene

Treatment
- thrombosis
  - lifelong anti-coagulation with warfarin
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent and/or arterial event
- recurrent fetal loss
- heparin/low molecular weight heparin ± Aspirin® during pregnancy
- catastrophic APLA
  - high-dose steroids, anti-coagulation, cyclophosphamide, plasmapheresis

Scleroderma

Definition
- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy and fibrosis

![Scleroderma](image)

Figure 8. Forms of scleroderma

<table>
<thead>
<tr>
<th>Localized</th>
<th>Generalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>(no involvement of internal organs)</td>
<td>(systemic sclerosis)</td>
</tr>
<tr>
<td>Mostly children and young adults</td>
<td>Limited systemic sclerosis</td>
</tr>
<tr>
<td>Morphea</td>
<td>Skin sclerosis restricted to hands, face, neck</td>
</tr>
<tr>
<td>Hard oval patches on the skin</td>
<td>3rd to 4th decade</td>
</tr>
<tr>
<td>Linear</td>
<td>Pulmonary HTN common</td>
</tr>
<tr>
<td>Line of thickened skin</td>
<td>CREST</td>
</tr>
</tbody>
</table>

| Diffuse systemic sclerosis | Widespread skin disease (proximal to wrist, can involve trunk), tendons |
| Early visceral involvement (renal, pulmonary fibrosis) |

Table 17. Classification Criteria of Systemic Sclerosis*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>Scleroderma proximal to MCPs Skin tightness, thickening, non-pitting induration</td>
</tr>
<tr>
<td>Minor</td>
<td>Sclerodactyly Skin changes limited to digits</td>
</tr>
<tr>
<td></td>
<td>Digital pitting scars or loss of substance from finger pad</td>
</tr>
<tr>
<td></td>
<td>Bibasilar pulmonary fibrosis</td>
</tr>
</tbody>
</table>

*Diagnosed if 1 major or 2 minor criteria must be present
American Rheumatism Association, 1980

Etiology and Pathophysiology
- idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues
  - intimal proliferation and media mucinous degeneration → progressive obliteration of vessel lumen → fibrotic tissue
  - resembles malignant HTN
Epidemiology
• F:M = 3-4:1, peaking in 5th and 6th decades
• associated with HLA-DR1
• associated with environmental exposure (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)
• limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)

Signs and Symptoms

Table 18. Clinical Manifestations of Scleroderma

<table>
<thead>
<tr>
<th>System</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>Painless non-pitting edema → skin tightening</td>
</tr>
<tr>
<td></td>
<td>Ulcerations, calcinosis, perungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias</td>
</tr>
<tr>
<td></td>
<td>Characteristic face: mask-like facies with tight lips, beak nose, radial perioral furrows</td>
</tr>
<tr>
<td>Vascular</td>
<td>Raynaud’s phenomenon → digital pits, gangrene</td>
</tr>
<tr>
<td>Gastrointestinal (&lt;90%)</td>
<td>Loss of lower esophageal sphincter function → GERD, ulcerations, strictures</td>
</tr>
<tr>
<td></td>
<td>Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss</td>
</tr>
<tr>
<td></td>
<td>Large bowel hypomotility → wide mouth diverticuli are pathognomonic radiographic finding on barium study</td>
</tr>
<tr>
<td>Renal</td>
<td>Mild proteinuria, Cr elevation, HTN</td>
</tr>
<tr>
<td></td>
<td>“Scleroderma renal crisis” (10-15%) may lead to malignant arterial HTN, oliguria, and microangiopathic hemolytic anemia</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Polyarthralgias</td>
</tr>
<tr>
<td></td>
<td>“Resorption of distal tufts” (radiological finding)</td>
</tr>
<tr>
<td></td>
<td>Proximal weakness 2° to disuse, atrophy, low grade myopathy</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypothyroidism</td>
</tr>
</tbody>
</table>

Investigations
• blood work
  - CBC, Cr, ANA
  - anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis
  - anti-centromere: favors diagnosis of CREST (limited systemic sclerosis)
• PFT
  - assess for pulmonary HTN or interstitial lung disease
• imaging
  - CXR for fibrosis, echo for pulmonary HTN

Treatment
• dermatologic
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), MTX (limited evidence)
• vascular
  - patient education on cold avoidance
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE2 inhibitors, PDE5 inhibitors)
• gastrointestinal
  - GERD: PPIs are first line, then H2-receptor agonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
• renal disease
  - ACE inhibitors for hypertensive crisis
• pulmonary
  - early interstitial disease: cyclophosphamide
  - pulmonary HTN: vasodilators e.g. bosentan (Tracleer®), epoprostenol (Flolan®), PDE5 inhibitors
• cardiac
  - pericarditis: systemic steroids
• musculoskeletal
  - arthritis: NSAIDs
  - myositis: systemic steroids

Raynaud’s Phenomenon DDx

COLD HAND
  - Cryoglobulins/Cryofibrinogens
  - Obstruction/Occupational
  - SLE erythematosus, other connective tissue disease
  - Diabetes mellitus/Drugs
  - Hematologic problems (polycythemia, leukemia, etc.)
  - Arterial problems (atherosclerosis)/Anorexia nervosa
  - Neurologic problems (vascular tone)
  - Disease of unknown origin (idiopathic)

Scleroderma is the most common cause of secondary Raynaud’s phenomenon

Lung disease is the most common cause of morbidity and mortality

Features of Pathologic Raynaud's Syndrome
• New onset
• Asymmetric
• Precipitated by stimuli other than cold or emotion
• Associated with distal pulp pitting or tissue reabsorption
• Digital ischemia
• Capillary dilatation by capillaroscopy
Idiopathic Inflammatory Myopathy

Definition
- autoimmune diseases characterized by proximal muscle weakness ± pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process

Classification
- PM/DMM
- adult and juvenile form
- associated with malignancy
  - increased risk of malignancy: age >50, DMM>PM, normal CK, refractory disease
  - 2.4-6.5 fold increased risk of underlying malignancy usually in internal organs
- associated with other connective tissue disease, Raynaud’s phenomenon, autoimmune disorders
- inclusion body myositis
  - age >50, M>F, slowly progressive, vacuoles in cells on biopsy
  - suspect when patient unresponsive to treatment
  - distal as well as proximal muscle weakness
  - muscle biopsy positive for inclusion bodies

POLYMYSITIS/DERMATOMYOSITIS

Table 19. Classification Criteria for PM/DMM

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symmetric proximal muscle weakness</td>
<td>Typical involvement of shoulder girdle and hip girdle</td>
</tr>
<tr>
<td>2. Elevated muscle enzymes</td>
<td>↑ CK, aldolase, LDH, AST, ALT</td>
</tr>
<tr>
<td>3. EMG changes</td>
<td>Short polyphasic motor units, high frequency repetitive discharge, insertional irritability</td>
</tr>
<tr>
<td>4. Muscle biopsy</td>
<td>Segmental fiber necrosis, basophilic regeneration, perivascular inflammation (DMM), endomysial inflammation (PM) and atrophy</td>
</tr>
<tr>
<td>5. Typical rash of dermatomyositis</td>
<td>Required for diagnosis of DMM (see below)</td>
</tr>
</tbody>
</table>

NEJM 1975;292:403-407

Etiology and Pathophysiology
- PM is CD8 cell-mediated muscle necrosis, found in adults
- DMM is B-cell and CD4 immune complex-mediated perifascicular vascular abnormalities

Signs and Symptoms
- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over weeks to months
  - difficulty lifting head off pillow, arising from chair, climbing stairs
- dermatological
  - DMM has characteristic dermatological features (F>M, children and adults)
    - Gottron’s papules
      - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
    - Gottron’s sign
      - erythematous, smooth or scaly patches over the dorsal IPs, MCPs, elbows, knees, or medial malleoli
    - heliotrope rash: violaceous rash over the eyelids, usually with edema
    - shawl sign: erythematous rash over neck, upper chest, and shoulders
    - mechanic’s hands: dark, dry, thick scale on palmar and lateral surface of digits
    - periungual erythema
- cardiac
  - dysrhythmias, CHF, conduction defect, ventricular hypertrophy, pericarditis
- gastrointestinal
  - oropharyngeal and lower esophageal dysphagia, reflux
- pulmonary
  - weakness of respiratory muscles, interstitial lung disease, aspiration pneumonia

Investigations
- blood work: CK, ANA, anti-Jo-1 (DMM), anti-Mi-2, anti-SRP
- imaging: MRI may be used to localize biopsy site
- EMG, muscle biopsy

Treatment
- non-pharmacological: physical therapy and occupational therapy
- pharmacological treatment
  - high-dose corticosteroid (1-2 mg/kg/d) and slow taper
  - add immunosuppressive agents (azathioprine, MTX, cyclosporine)
  - intravenous immunoglobulin if severe or refractory
  - hydroxychloroquine for DMM rash

Signs of DMM
Gottron’s papules and Gottron’s sign are pathognomonic of DMM (occur in 70% of patients)
• malignancy surveillance
  ▪ detailed history and physical (breast, pelvic, and rectal exam)
  ▪ CXR, abdominal and pelvic U/S, fecal occult blood, Pap test, mammogram ± CT scan (thoracic, abdominal, pelvic)

**Sjögren’s Syndrome**

**Definition**
• autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca/xerophthalmia) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
• may evolve into systemic disorder with diminished exocrine gland activity in respiratory tract and skin
• primary and secondary form (associated with RA, SLE, DMM, and HIV)
• incidence estimated at 4/100,000 people
• 90% of cases are among females
• mean age of diagnosis is 40-60 yr

**Table 20. Classification Criteria for SS**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dry eye symptoms</td>
<td>Dry &gt;3 mo, foreign body sensation, or requiring tear substitutes</td>
</tr>
<tr>
<td>2. Dry mouth symptoms</td>
<td>Dry &gt;3 mo, swollen salivary glands, or requiring liquids to swallow food</td>
</tr>
<tr>
<td>3. Dry eye signs</td>
<td>Schirmer test (to assess tear flow) or slit lamp exam with Rose Bengal stain</td>
</tr>
<tr>
<td>4. Dry mouth signs</td>
<td>Low salivary flow, sialography</td>
</tr>
<tr>
<td>5. Salivary gland biopsy</td>
<td>Focal lymphocytic sialoadenitis</td>
</tr>
<tr>
<td>6. Autoantibodies</td>
<td>anti-Ro and/or anti-La, ANA, RF</td>
</tr>
</tbody>
</table>

*S* Diagnosed if 4 of the above criteria present, one of which includes salivary gland biopsy or autoantibodies

**Signs and Symptoms**
• "sicca complex": dry eyes (keratoconjunctivitis sicca/xerophthalmia), dry mouth (xerostomia)
• staphylococcus blepharitis
• dental caries, oral candidiasis, angular cheilitis (inflammation and fissuring at the labial commissures of the mouth)
• systemic complications
  ▪ sinusitis, autoimmune thyroid dysfunction
  ▪ arthralgias, arthritis
  ▪ subclinical diffuse interstitial lung disease, xerotrachea leading to chronic dry cough
  ▪ renal disease, glomerulonephritis
  ▪ palpable purpura, vasculitis
  ▪ peripheral neuropathy
  ▪ lymphoma risk greatly increased

**Treatment**
• ocular
  ▪ artificial tears or surgical punctal occlusion for dry eyes
• oral
  ▪ good dental hygiene, hydration
  ▪ agents that stimulate salivary flow (e.g. pilocarpine)
  ▪ topical nystatin or clotrimazole x 4-6 wk for oral candidiasis
• systemic
  ▪ e.g. hydroxychloroquine, corticosteroids

**Mixed Connective Tissue Disease**
• syndrome with features of 3 different connective tissue diseases (e.g. SLE, scleroderma, PM)
• common symptoms: Raynaud’s phenomenon, swollen fingers
• blood work: anti-RNP (see Table 10)
• treatment is generally guided by the severity of symptoms and organ system involvement
• prognosis
  ▪ 50-60% will evolve into SLE
  ▪ 40% will evolve into scleroderma
  ▪ only 10% will remain as MCTD for the rest of their lives
  ▪ cardiac involvement (dysrhythmia) common, renal or lung involvement rare

**Overlap Syndrome**
• syndrome with sufficient diagnostic features of 2+ different connective tissue diseases
Vasculitides

- inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction
- any organ system can be involved
- keys to diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection
  - labs non-specific: anemia, increased WBC and ESR, abnormal U/A
  - biopsy if tissue accessible
  - angiography if tissue inaccessible
- treatment generally involves corticosteroids and/or immunosuppressive agents

Table 21. Classification of Vasculitis and Characteristic Features

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMALL VESSEL</td>
<td></td>
</tr>
<tr>
<td>• Non-ANCA-Associated</td>
<td></td>
</tr>
<tr>
<td>- Predominantly cutaneous vasculitis</td>
<td>Also known as hypersensitivity/leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>- Henoch-Schönlein purpura (see Pediatrics, P96)</td>
<td>Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal, usually self-limiting; most common in childhood</td>
</tr>
<tr>
<td>- Essential cryoglobulinemic vasculitis</td>
<td>Systemic vasculitis caused by circulating cryoproteins forming immune complexes; may be associated with underlying infection (e.g. hepatitis C) or connective tissue disease</td>
</tr>
<tr>
<td>• ANCA-Associated</td>
<td></td>
</tr>
<tr>
<td>- Granulomatosis with polyangitis (GPA, formerly Wegener’s)</td>
<td>Granulomatous inflammation of vessels of respiratory tract and kidneys, initially have URTI symptoms; most common in middle age</td>
</tr>
<tr>
<td>- Eosinophilic granulomatosis with polyangitis (Churg-Strauss syndrome) (50% ANCA positive)</td>
<td>Granulomatous inflammation of vessels with hypereosinophilia and eosinophilic tissue infiltration, frequent lung involvement (asthma, allergic rhinitis), can be associated with MPO or pR3, other manifestations include coronary arteritis, myocarditis and neuropathy, average age 40s</td>
</tr>
<tr>
<td>- Microangiopathic polyangitis (70% ANCA positive, usually MPO)</td>
<td>Pauci-immune necrotizing vasculitis, affecting kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin, most common in middle age</td>
</tr>
<tr>
<td>MEDIUM VESSEL</td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Segmental, non-granulomatous necrotizing inflammation Unknown etiology in most cases, any age (average 40-50s), M&gt;F</td>
</tr>
<tr>
<td>Kawasaki disease (see Pediatrics, P96)</td>
<td>Arteritis and mucocutaneous lymph node syndrome</td>
</tr>
<tr>
<td>LARGE VESSEL</td>
<td></td>
</tr>
<tr>
<td>GCA/Temporal arteritis</td>
<td>Inflammation predominantly of the aorta and arteries originating from it &gt;50 yr of age, F&gt;M</td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>“Pulseless disease”, unequal peripheral pulses, chronic inflammation, most often the aorta and its branches Usually young adults of Asian descent, F&gt;M; risk of aortic aneurysm</td>
</tr>
<tr>
<td>OTHER VASCULITIDES</td>
<td></td>
</tr>
<tr>
<td>Buerger’s disease (“Thromboangiitis Obliterans”)</td>
<td>Inflammation secondary to pathological clotting, affects small and medium-sized vessels of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking Most common in young Asian males</td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Leukocytoclastic vasculitis, multi-system disorder presenting with ocular involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis, skin and joint involvement, more common in Mediterranean and Asia, average age 30s, M&gt;F</td>
</tr>
<tr>
<td>Vasculitis mimicry</td>
<td>Cholesterol emboli, atrial myxoma</td>
</tr>
</tbody>
</table>

c-ANCA: circulating anti-neutrophil cytoplasmic Ab associated with anti-pR3
p-ANCA: perinuclear anti-neutrophil cytoplasmic Ab associated with multiple antigens, e.g. lactoferrin (IBD), myeloperoxidase (microscopic polyangiitis)

Churg-Strauss Triad
- Allergic rhinitis and asthma (often quiescent at time of vasculitis)
- Eosinophilic infiltrative disease resembling pneumonia
- Systemic vasculitis often mononeuritis multiplex/peripheral neuropathy and peripheral eosinophilia

Features of Small Vessel Vasculitis
- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers

Features of Medium Vessel Vasculitis
- Livedo reticularis
- Erythema nodosum
- Raynaud’s phenomenon
- Nodules
- Digital infarcts
- Ulcers
Small Vessel Non-ANCA Associated Vasculitis

PREDOMINANTLY CUTANEOUS VASCULITIS
- subdivided into
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases

Etiology and Pathophysiology
- cutaneous vasculitis following
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes
- small vessels involved (post-capillary vessels most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Signs and Symptoms
- palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules
  - renal or joint involvement may occur, especially in children

Investigations
- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment
- stop possible offending drug
- corticosteroids ± immunosuppressive agents
- usually self-limiting

Small Vessel ANCA-Associated Vasculitis

GRANULOMATOSIS WITH POLYANGIITIS (GPA, formerly known as Wegener’s Granulomatosis)

Definition
- granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
- highly associated with c-ANCA
- incidence 5 per 100,000; more common in Northern latitudes

Table 22. Classification Criteria for GPA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nasal or oral involvement</td>
<td>Inflammation, ulcers, epistaxis</td>
</tr>
<tr>
<td>2. Abnormal findings on CXR</td>
<td>Nodules, cavitations, etc.</td>
</tr>
<tr>
<td>3. Urinary sediment</td>
<td>Microscopic hematuria ± RBC casts</td>
</tr>
<tr>
<td>4. Biopsy of involved tissue</td>
<td>Lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis</td>
</tr>
</tbody>
</table>

*Diagnosed if 2 or more of the above 4 criteria present
American College of Rheumatology, 1990
Etiology
- pathogenesis depends on genetic susceptibility and environmental triggers (e.g. infection)
  - dysregulated immune response due to loss of B and T-cell tolerance
  - acute vascular injury mediated by neutrophils and monocytes

Signs and Symptoms
- systemic
  - malaise, fever, weakness, weight loss
- HEENT
  - sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
  - proptosis due to: inflammation/vasculitis involving extra-ocular muscles, granulomatous retrobulbar space occupying lesions or direct extension of masses from the upper respiratory tract
  - hearing loss due to involvement of CN VIII
- pulmonary
  - cough, hemoptysis, granulomatous upper respiratory tract masses
- renal
  - hematuria
- other
  - joint, skin, eye complaints, vasculitic neuropathy

Investigations
- blood work: anemia (normal MCV), increased WBC, increased Cr, increased ESR, elevated platelet count, ANCA (PR3 > MPO)
- U/A: proteinuria, hematuria, RBC casts
- CXR: pneumonitis, lung nodules, infiltrations, cavitary lesions
- biopsy: renal (segmental necrotizing glomerulonephritis), lung (granulomas, tracheobronchial erosion)
- possible decline in c-ANCA and ESR used to monitor response to treatment in some patients

Treatment
- prednisone 1 mg/kg/d PO for 3-6 mo ± cyclophosphamide 2 mg/kg/d PO for 3-6 mo followed by high dose MTX (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/d PO OD)
- consider biologic agents (rituximab, IVIg) and plasmapheresis (PEXIVAS trial)
- RAVE trial (NEJM 2010;363:221-232): rituximab equivalent or superior to cyclophosphamide in severe or relapsing disease

Medium Vessel Vasculitis

POLYARTERITIS NODOSA

Definition
- systemic, necrotizing vasculitis of medium sized vessels
- ANCA negative
- often associated with hepatitis B positivity
- incidence 0.7 per 100,000; affects individuals between 40-60 yr; M:F = 2:1

Table 23. Classification Criteria for PAN*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight loss</td>
<td>&gt;4 kg, not due to dieting or other factors</td>
</tr>
<tr>
<td>2. Myalgias, weakness, or leg tenderness</td>
<td>Diffuse myalgias or weakness</td>
</tr>
<tr>
<td>3. Livedo reticularis</td>
<td>Mottled, reticular pattern over skin</td>
</tr>
<tr>
<td>4. Neuropathy</td>
<td>Mononeuropathy, mononeuropathy multiplex, or polyneuropathy</td>
</tr>
<tr>
<td>5. Testicular pain or tenderness</td>
<td>Not due to infection, trauma, or other causes</td>
</tr>
<tr>
<td>6. dBP &gt;90 mmHg</td>
<td>Development of HTN with dBP &gt;90 mmHg</td>
</tr>
<tr>
<td>7. Elevated Cr or BUN</td>
<td>Cr &gt;130 μmol/L (1.5 mg/dL), BUN &gt;14.3 mmol/L (40 mg/dL)</td>
</tr>
<tr>
<td>8. Hepatitis B positive</td>
<td>Presence of hepatitis B surface antigen or Ab</td>
</tr>
<tr>
<td>9. Arteriographic abnormality</td>
<td>Commonly aneurysms</td>
</tr>
<tr>
<td>10. Biopsy of artery</td>
<td>Presence of granulocytes and/or mononuclear leukocytes in the artery wall</td>
</tr>
</tbody>
</table>

*Diagnosed if 3 or more of the above 10 criteria present.
American College of Rheumatology, 1990

Medium Vessel Vasculitis

POLYARTERITIS NODOSA

Definition
- systemic, necrotizing vasculitis of medium sized vessels
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</tr>
<tr>
<td>3. Livedo reticularis</td>
<td>Mottled, reticular pattern over skin</td>
</tr>
<tr>
<td>4. Neuropathy</td>
<td>Mononeuropathy, mononeuropathy multiplex, or polyneuropathy</td>
</tr>
<tr>
<td>5. Testicular pain or tenderness</td>
<td>Not due to infection, trauma, or other causes</td>
</tr>
<tr>
<td>6. dBP &gt;90 mmHg</td>
<td>Development of HTN with dBP &gt;90 mmHg</td>
</tr>
<tr>
<td>7. Elevated Cr or BUN</td>
<td>Cr &gt;130 μmol/L (1.5 mg/dL), BUN &gt;14.3 mmol/L (40 mg/dL)</td>
</tr>
<tr>
<td>8. Hepatitis B positive</td>
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</tr>
<tr>
<td>10. Biopsy of artery</td>
<td>Presence of granulocytes and/or mononuclear leukocytes in the artery wall</td>
</tr>
</tbody>
</table>

*Diagnosed if 3 or more of the above 10 criteria present.
American College of Rheumatology, 1990
Etiology and Pathophysiology
- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion

Investigations
- blood work: CBC, ESR, Cr, BUN, p-ANCA, hepatitis B serology
- imaging: angiography
- arterial biopsy

Treatment
- prednisone 1 mg/kg/d PO and cyclophosphamide 2 mg/kg/d PO
- ± anti-viral therapy to enhance clearance of hepatitis B virus

Large Vessel Vasculitis
- see Neurology, N44 and Ophthalmology, OP38 for more details

GCA/TEMPORAL ARTERITIS

Table 24. Classification Criteria for GCA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age at onset ≥50</td>
<td></td>
</tr>
<tr>
<td>2. New headache</td>
<td>Often temporal</td>
</tr>
<tr>
<td>3. Temporal artery abnormality</td>
<td>Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis</td>
</tr>
<tr>
<td>4. Elevated ESR</td>
<td>ESR ≥50 mm/h</td>
</tr>
<tr>
<td>5. Abnormal artery biopsy</td>
<td>Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
</tr>
</tbody>
</table>

*Diagnosed if 3 or more of the above 5 criteria present
American College of Rheumatology, 1990

Epidemiology
- most frequent vasculitis in North America
- patients >50 yr
- F:M = 2:1
- North-South gradient (predominance in Northern Europe/US)
- affects extracranial arteries

Signs and Symptoms
- new onset temporal headache ± scalp tenderness due to inflammation of involved portion of the temporal or occipital arteries
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
- tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
- PMR (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta result in pulseless disease), aortic aneurysm ± rupture are late complications

Investigations
- diagnosis made by clinical suspicion, increased ESR, increased CRP, temporal artery biopsy within 14 d of starting steroids, possible U/S

Treatment
- if suspect GCA, immediately start high dose prednisone 1 mg/kg in divided doses for approximately 4 wk, and then tapering prednisone as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
- consider low dose ASA

Prognosis
- increased risk of thoracic aortic aneurysm and aortic dissection
- yearly CXR ± abdominal U/S as screening

Medical Emergency
Untreated, GCA can lead to permanent blindness in 20-25% of patients; treat on clinical suspicion

GCA Criteria
Presence of 3 or more criteria yields sensitivity of 94%, specificity of 91%
SERONEGATIVE RHEUMATIC DISEASE

Spondyloarthropathies

Table 25. A Comparison of the Spondyloarthropathies (inflammatory joint disease of the vertebral column)

<table>
<thead>
<tr>
<th>Feature</th>
<th>AS</th>
<th>PsA</th>
<th>ReA</th>
<th>EA</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>3:1</td>
<td>1:1</td>
<td>8:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>20s</td>
<td>35-45</td>
<td>20s</td>
<td>Any</td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td>25%</td>
<td>96%</td>
<td>90%</td>
<td>Common</td>
</tr>
<tr>
<td>Distribution</td>
<td>Axial, LE</td>
<td>Any</td>
<td>LE</td>
<td>LE</td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>100%</td>
<td>40%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Uncommon</td>
<td>Common</td>
<td>Occasional</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Less Common</td>
</tr>
<tr>
<td>Skin Lesions</td>
<td>Rare</td>
<td>100% Psoriasis eventually 70% at onset of arthritis</td>
<td>Common Keratoderma</td>
<td>Occasional Pyoderma, erythema nodosum</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Common</td>
<td>Occasional</td>
<td>20%</td>
<td>Rare</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>90%</td>
<td>40%</td>
<td>80%</td>
<td>30%</td>
</tr>
</tbody>
</table>

LE = lower extremities

Ankylosing Spondylitis

Definition
- chronic inflammatory arthritis involving the sacroiliac joints and vertebrae
- AS in women: more peripheral arthritis and upper spine spondylitis
- prototype of the spondyloarthropathies

Table 26. ASAS Classification Criteria for Axial Spondyloarthritis*

| Sacroiliitis on imaging plus ≥1 AS feature or HLA-B27 positive plus ≥2 AS features |
|-----------------------------------|-----------------------------------|-----------------------------------|
| AS features:                      | Sacroiliitis on imaging:          |
| • Inflammatory back pain          | • Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with AS |
| • Arthritis                       | • Definite radiographic sacroiliitis ≥ grade 2 bilaterally or grade 3-4 unilaterally |
| • Enthesitis (heel)               |                                   |
| • Uveitis                         |                                   |
| • Dactylitis                      |                                   |
| • Psoriasis                       |                                   |
| • Crohn’s disease/collitis        |                                   |
| • Good response to NSAIDs         |                                   |
| • Family history of AS            |                                   |
| • HLA-B27 positive                |                                   |
| • Elevated CRP                    |                                   |

*For patients with ≥3 mo back pain and age at onset <45 yr

Etiology and Pathophysiology
- enthesitis (inflammation of tendon or ligament at site of attachment to bone)
- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

Epidemiology
- M:F = 5:1; females have milder disease which may be under-recognized
- 95% of patients have HLA-B27 (9% HLA-B27 positive in general population)
Table 27. Types of Back Pain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mechanical</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past History</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Family History</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Age</td>
<td>15-90 yr</td>
<td>&lt;40 yr</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>±</td>
<td>++ (worse during 2nd half of night)</td>
</tr>
<tr>
<td>Morning Stiffness</td>
<td>&lt;30 min</td>
<td>&gt;1 h</td>
</tr>
<tr>
<td>Involvement of Other Systems</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Exercise</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Rest</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Radiation of Pain</td>
<td>Anatomic (L5-S1)</td>
<td>Diffuse (thoracic, buttock)</td>
</tr>
<tr>
<td>Sensory Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Motor Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

Signs and Symptoms

- **axial**
  - mid and lower back stiffness, prolonged morning stiffness, night pain, persistent buttock pain, painful sacroiliac joint (+ Faber test)
  - spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion, normal >5 cm at T4), cervical (global decrease, often extension first)
  - postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance (>5 cm)

- **peripheral**
  - asymmetrical large joint arthritis, most often involving lower limb
  - enthesitis: tenderness over tibial tuberosity, or Achilles tendon and plantar fascia insertions into the calcaneus

- **extra-articular manifestations**
  - ophthalmic: acute anterior uveitis is common (25-30% patients)
  - renal: amyloidosis (late and rare) and IgA nephropathy
  - gastrointestinal: IBD
  - cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare)
  - respiratory: apical fibrosis (rare)
  - neurologic: cauda equina syndrome (rare)
  - skin: psoriasis

Investigations

- x-ray of SI joint: “pseudowidening” of joint due to erosion with joint sclerosis → bony fusion (late), symmetric sacroiliitis
- x-ray of spine: “squaring of edges” from erosion and sclerosis on corners of vertebral bodies (shiny corner sign) leading to ossification of outer fibers of annulus fibrosis (bridging syndesmophytes) → “bamboo spine” radiographically
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes. Best seen on T2 STIR images (suppress fat and see bone edema)

Treatment

- **conservative/non-pharmacologic**
  - prevent fusion from poor posture and disability through: exercise (e.g. swimming), postural and deep breathing exercises, outpatient PT, smoking cessation
- **medical**
  - NSAIDs (first line of treatment)
  - glucocorticoids (topical eye drops, local injections)
  - DMARDs for peripheral arthritis (sulfasalazine, MTX)
  - biologics for axial and peripheral involvement
  - manage extra-articular manifestations
- **surgical**
  - hip replacement, vertebral osteotomy for marked deformity

Prognosis

- spontaneous remissions and relapses are common and can occur at any age
- function may be excellent despite spinal deformity
- favorable prognosis if female and age of onset >40 yr
- early onset with hip disease may lead to severe disability; may require arthroplasty

Consider AS in the differential for causes of aortic regurgitation
Enteropathic Arthritis

- see Gastroenterology: Inflammatory Bowel Disease, G19
- MSK manifestations in the setting of either ulcerative colitis or Crohn’s disease include peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthropathy
- non-arthritic MSK manifestations can occur 2° to steroid treatment of bowel inflammation (arthralgia, myalgia, osteoporosis, AVN)
- NSAIDs should be used cautiously as they may exacerbate bowel disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spondylitis</th>
<th>Peripheral Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27 Association</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gender</td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td>Onset Before IBD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Parallels IBD Course</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Type of IBD</td>
<td>UC=CD</td>
<td>CD</td>
</tr>
</tbody>
</table>

Psoriatic Arthritis

Etiology and Pathophysiology

- unclear but many genetic, immunologic, and some environmental factors involved (e.g. psoriatic plaque flora, particularly Group A Streptococcus, and trauma)

Epidemiology

- psoriasis affects 1% of population
- arthropathy in 10% of patients with psoriasis
- 15-20% of patients will develop joint disease before skin lesions appear

Signs and Symptoms

- dermatologic
  - well-demarcated erythematous plaques with silvery scale
  - nail involvement: pitting, transverse or longitudinal ridging, discoloration, subungual hyperkeratosis, onycholysis, and oil drops
- musculoskeletal
  - 5 general patterns
    - asymmetric oligoarthritis (most common – 70%)
    - arthritis of DIP joints with nail changes
    - destructive (mutlans) arthritis (5%)
    - symmetric polyarthritis (similar to RA)
    - sacroiliitis and spondylitis (usually older, male patients)
  - other findings: dactylitis, enthesopathy
- ophthalmic
  - conjunctivitis, iritis (anterior uveitis)
- cardiac and respiratory (late findings)
  - aortic insufficiency
  - apical lung fibrosis
- neurologic
  - cauda equina syndrome
- radiologic
  - floating syndesmophytes
  - pencil-in-cup appearance at IP joints
  - osteolysis, periostitis

Treatment

- treat skin lesions (e.g. steroid cream, salicylic and/or retinoic acid, tar, UV light)
- NSAIDs or IA steroids
- DMARDs, biologic therapies to minimize erosive disease (use early if peripheral joint involvement)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of psoriasis</td>
<td>Current, past, or family history</td>
</tr>
<tr>
<td>2. Psoriatic nail dystrophy</td>
<td>Onycholysis, pitting, hyperkeratosis</td>
</tr>
<tr>
<td>3. Negative results for RF</td>
<td>Current or past history</td>
</tr>
<tr>
<td>4. Dactylitis</td>
<td>Juxta articular bone formation on hand or foot x-rays</td>
</tr>
<tr>
<td>5. Radiological evidence</td>
<td></td>
</tr>
</tbody>
</table>

*To meet the CASPAR (Classification criteria for Psoriatic Arthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or entheses) with ≥3 points from the above 5 categories
**Reactive Arthritis**

**Definition**
- two meanings
  1. ReA: a sterile arthritis following an infection (e.g. rheumatic fever, post-viral arthritis, etc.), not used frequently by rheumatologists
  2. ReA: one of the seronegative spondyloarthropathies in which patients have a peripheral arthritis (≥1 mo duration) accompanied by one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tracts

**Etiology**
- onset following an infectious episode either involving the GI or GU tract
  - GI: *Shigella, Salmonella, Campylobacter, Yersinia* species
  - GU: *Chlamydia* (isolated in 16-44% of ReA cases), *Mycoplasma* species
- acute clinical course
  - 1-4 wk post-infection
  - lasts weeks to years
  - often recurring
  - spinal involvement persists

**Epidemiology**
- in HLA-B27 patients, axial > peripheral involvement
- M>F

**Signs and Symptoms**
- musculoskeletal
  - peripheral arthritis, asymmetric pattern, spondylitis, Achilles tendinitis, plantar fasciitis, dactylitis
- ophthalmic
  - iritis (anterior uveitis), conjunctivitis
- dermatologic
  - keratoderma blenorrhagicum (hyperkeratotic skin lesions on palms and soles) and balanitis cincturata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- gastrointestinal
  - oral ulcers, diarrhea
- urethritis and cervicitis
  - sterile cultures; presence not related to site of initiating infection

**Investigations**
- diagnosis is clinical plus laboratory
- blood work: normocytic, normochromic anemia, and leukocytosis
- sterile cultures
- serology: HLA-B27 positive

**Treatment**
- antibiotics for non-articular infections
- NSAIDs, physical therapy, exercise
- local therapy
  - joint protection
  - IA steroid injection
  - topical steroid for ocular involvement
- systemic therapy
  - corticosteroids, sulfasalazine, MTX (for peripheral joint involvement only)
  - TNF-α inhibitors for spinal inflammation

**Prognosis**
- self-limited, typically 3-5 mo, varies based on pathogen and patient's genetic background
- chronic in 15-20% of cases

---

**Crystal-Induced Arthropathies**

**Table 30. Gout vs. Pseudogout**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td>Age</td>
<td>Middle-aged males</td>
<td>Age &gt;60 yr</td>
</tr>
<tr>
<td></td>
<td>Post-menopausal females</td>
<td></td>
</tr>
<tr>
<td>Onset of Disease</td>
<td>Acute</td>
<td>Acute/insidious</td>
</tr>
<tr>
<td>Crystal Type</td>
<td>Monosodium urate (MSU)</td>
<td>Calcium pyrophosphate dihydrate (CPPD)</td>
</tr>
<tr>
<td></td>
<td>Negative birefringence (yellow when parallel to compensator filter), needle-shaped</td>
<td>Positive birefringence (blue when parallel), rhomboid-shaped</td>
</tr>
</tbody>
</table>
Gout

Definition
• derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

Etiology and Pathogenesis
• sources of uric acid: diet and endogenous
  • hypoxanthine → xanthine → uric acid
• both steps catalyzed by xanthine oxidase

Hyperuricemia
• primary or genetic
  • mostly due to idiopathic renal underexcretion (90%)
  • also idiopathic overproduction or abnormal enzyme production/function
• secondary
  • dietary excess (particularly high consumption of beer, seafood, and meat)
  • underexcretion (>90%): renal failure, drugs, systemic conditions
  • overproduction (<10%): increased nucleic acid turnover states (e.g. malignancy, post-chemotherapy)
• sudden changes (increasing or decreasing) in uric acid concentration are more important than absolute values
• acute gout can occur with normal serum uric acid
• changes in pH, temperature, or initiation of antihyperuricemics may precipitate an acute gouty attack

• common precipitants: alcohol, dietary excess, dehydration, drugs (e.g. thiazide and loop diuretics), trauma, illness, surgery, starting xanthine oxidase inhibitor therapy
• other associated conditions: HTN, obesity, DM, starvation

Epidemiology
• most common in males >45 yr old
• extremely rare in premenopausal females

Signs and Symptoms
• single episode progressing to recurrent episodes of acute inflammatory arthritis
• acute gouty arthritis
  • severe pain, redness, joint swelling, usually involving lower extremities
  • joint mobility may be limited
  • attack will subside spontaneously within several days to weeks; may recur
• tophi
  • urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
  • common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
• kidney
  • gouty nephropathy
  • uric acid calculi

Investigations
• joint aspirate: >90% of joint aspirates show crystals of monosodium urate (see Table 30) (negatively birefringent, needle-shaped)
• x-rays may show tophi as soft tissue swelling, punched-out lesions — erosion with “over-hanging” edge

Treatment
• acute gout
  • NSAIDs: high dose, then taper as symptoms improve
  • corticosteroids: IA, oral, or intra-muscular (if renal, cardiovascular, or GI disease and/or if NSAIDs contraindicated or failed)
  • colchicine within first 12 h but effectiveness limited by narrow therapeutic range
  • allopurinol can worsen an acute attack (do not start during acute flare)
• chronic gout
  • conservative
    • avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
    • avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)

Table 30. Gout vs. Pseudogout (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>First MTP classically; also midfoot, ankle, knee, or polyarticular</td>
<td>Knee, wrist; monoarticular or polyarticular if chronic</td>
</tr>
<tr>
<td>Radiology</td>
<td>Erosions</td>
<td>Chondrocalcinosis</td>
</tr>
<tr>
<td>Treatment</td>
<td>NSAIDs, corticosteroids, colchicine</td>
<td>NSAIDs, corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Allopurinol, febuxistat (chronic)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 12. Common sites of involvement in gout
(asymmetric joint involvement)

1. Identification of monosodium urate crystals should be performed for a definitive diagnosis of gout.
2. Gout/hyperuricemia should prompt investigations of renal function and GI risk factors.
3. Acute gout should be treated with colchicine, NSAIDs, and/or glucocorticoids.
4. Patients should be counseled about lifestyle.
5. Allopurinol is first line forurate-lowering therapy, with allopurinol as second line.
6. Patients should be informed about the risk of acute gout flare with initiation of urate lowering therapy; colchicine prophylaxis should be considered.
7. Allopurinol can be used in patients with mild/moderate renal impairment with close titration and monitoring.
8. Treatment goal is urate <0.36 mM and absence of attacks and resolution of tophi.
9. Tophi should be treated medically by lowering serum urate to <0.3 mM. Surgery is only for select cases.
10. Prophylactic pharmacological management of asymptomatic hyperuricemia is not recommended.
• medical
  • antihyperuricemic drugs (allopurinol and febuxostat): decrease uric acid production by
    inhibiting xanthine oxidase
  • uricosuric drugs (probenecid, sulfinpyrazone): use if failure on or intolerant to
    allopurinol; do not use in renal failure
• prophylaxis prior to starting antihyperuricemic drugs (colchicine/low-dose NSAID)
• in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor Cr

indications for treatment with antihyperuricemic medications include:
• recurrent attacks, tophi, bone erosions, urate kidney stones
• perhaps in renal dysfunction with very high urate load (controversial)

Pseudogout (Calcium Pyrophosphate Dihydrate Disease)

Etiology and Pathophysiology
• acute inflammatory arthritis due to phagocytosis of IgG-coated CPPD crystals by neutrophils
  and subsequent release of inflammatory mediators within joint space
• more frequently polyarticular
• slower in onset in comparison to gout, lasts up to 3 wk but is self-limited

Risk Factors
• old age, advanced OA, neuropathic joints
• other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), DM, hemochromatosis

Signs and Symptoms
• affects knees, wrists, MCPs, hips, shoulders, elbows, ankles, big toe
• multiple manifestations
  • asymptomatic crystal deposition (seen on radiograph only)
  • acute crystal arthritis (self-limited flares of acute inflammatory arthritis resembling gout)
  • pseudo-OA (progressive joint degeneration, sometimes with episodes of acute inflammatory arthritis)
  • pseudo-RA (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
• acute may be triggered by dehydration, acute illness, surgery, trauma

Investigations
• must aspirate joint to rule out septic arthritis, gout
• CPPD crystals: present in 60% of patients, often only a few crystals
• x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

Treatment
• joint aspiration, rest, and protection
• NSAIDs: also used for maintenance therapy
• prophylactic colchicine PO (controversial)
• IA or oral steroids to relieve inflammation

Pediatric Rheumatology

• see Pediatrics, P93

Non-Articular Rheumatism

Definition
• disorders that primarily affect soft tissues or periarticular structures
• includes bursitis, tendinitis, tenosynovitis, fibromyalgia, and PMR

Polymyalgia Rheumatica

Definition
• characterized by pain and stiffness of the proximal extremities (girdle area)
• closely related to GCA (15% of patients with PMR develop GCA)
• no muscle weakness
Table 31. PMR Classification Criteria Scoring Algorithm*

<table>
<thead>
<tr>
<th>Points without U/S</th>
<th>Points with Abnormal U/S*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Required criteria: age ≥50 yr, bilateral shoulder aching, and abnormal ESR/CRP
**A score of 4 or more is categorized as PMR in the algorithm without U/S and a score of 5 or more is categorized as PMR in the algorithm with U/S

**Optional US criteria

Epidemiology

- incidence 50 per 100,000 per year in those >50 yr
- age of onset typically ≥50, F:M = 2:1

Signs and Symptoms

- constitutional symptoms prominent (fever, weight loss, malaise)
- pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs)
- gel phenomenon (stiffness after prolonged inactivity)
- physical exam reveals tender muscles, but no weakness or atrophy

Investigations

- blood work: often shows anemia, elevated platelets, elevated ESR and CRP, and normal CK; up to 5% of PMR reported with normal inflammatory markers

Treatment

- goal of therapy: symptom relief
- start with prednisone dose of 15-20 mg PO OD
- taper slowly over 2 yr period monitoring ESR and symptoms closely
- relapses should be diagnosed and treated on clinical basis; do not treat a rise in ESR as a relapse
- treat relapses aggressively (50% relapse rate)
- monitor for steroid side effects, glucocorticoid-induced osteoporosis prevention, and follow for symptoms of GCA

Fibromyalgia

Definition

- chronic (>3 mo), widespread (axial, left- and right-sided, upper and lower segment), non-articular pain with characteristic tender points

Diagnosis

2010 Diagnostic Criteria for Fibromyalgia

1. widespread pain index ≥7 and symptom severity score ≥5 or WPI 3-6 and SS ≥9
2. symptoms have been present at a similar level for ≥3 mo
3. the patient does not have a disorder that would otherwise explain the pain
   - widespread pain index = number of areas in which the patient had pain over the last week (L and R: shoulder girdle, upper arm, lower arm, hip, upper leg, lower leg, jaw, chest, abdomen, upper and lower back, neck = max score 19)
   - symptom severity score = sum of a) severity of fatigue, b) waking unrefreshed, and c) cognitive symptoms over the past week, plus d) extent of somatic symptoms (IBS, H/A, abdominal pain/ cramps, dry mouth, fever, hives, ringing in ears, vomiting, heartburn, dry eyes, SOB, loss of appetite, rash, hair loss, easy bruising, etc.); all (a-d) rated on 0-3 scale:
     0 = no problem, 1 = mild, 2 = moderate, 3 = severe
- this clinical definition identified 88.1% of American College of Rheumatology classified fibromyalgia and can allow longitudinal assessment of symptom severity

Epidemiology

- F:M = 3:1
- primarily ages 25-45 yr, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness
Signs and Symptoms
- widespread aching, stiffness
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent wakening
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- neurologic symptoms of hyperalgesia, paresthesias
- associated with irritable bowel or bladder syndrome, migraines, tension headaches, restless legs syndrome, obesity, depression, and anxiety
- physical exam should reveal only tenderness with palpation of soft tissues, with no specificity for trigger/tender points

Investigations
- blood work: includes TSH and ESR; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

Differential Diagnosis
- diagnosis of exclusion
- rule out other disorders by history and physical exam

Treatment
- conservative
  - education
  - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
  - stress reduction, CBT
  - no evidence for alternative medicine such as biofeedback, meditation, acupuncture
- medical
  - low dose tricyclic antidepressant (e.g. amitriptyline)
    - for sleep restoration
  - select those with lower anticholinergic side effects
  - SNRI: duloxetine, milnacipran
  - anticonvulsant: pregabalin, gabapentin
  - analgesics may be beneficial for pain that interferes with sleep (NSAIDs, not narcotics)

Prognosis
- variable; usually chronic, unless diagnosed and treated early

Adult Onset Still’s Disease

Definition
- systemic inflammatory condition (ANA and RF negative) with fevers and characteristic rash, numerous systemic symptoms, and may have severe arthritis

Etiology and Pathophysiology
- idiopathic; infectious triggers likely – various viruses and bacteria have been implicated
- stress increases risk

Epidemiology
- F>M; age of onset typically 16-40, approximately 1 per 100,000

Signs and Symptoms
- classic triad of symptoms
  - high-spiking fevers (95.7% of patients, typically T = 102.2°F/39°C, <4 h duration, quotidian pattern)
  - characteristic “salmon rash” (~72% of patients, on proximal limbs + trunk)
  - arthralgia/arthritis (64-100%)
  - sore throat, myalgias and serositis may also occur
  - arthritis is symmetric, typically affects large joints, i.e. wrists, knees and ankles, may involve PIP and DIPs, elbow, MTPs
  - liver abnormalities ± hepatomegaly (50-75% patients)
  - splenomegaly (44%)

Definition
- 39-41°C fever: <48 h duration, 3 episodes within 12 weeks
- rash: non-blanching, “salmon pink” on trunk, proximal extremities
- arthritis: symmetric, typically large joints

Signs and Symptoms
- high spiking fevers (95.7% of patients, typically T = 102°F/39°C, <4 h duration, quotidian pattern)
- characteristic “salmon rash” (~72% of patients, on proximal limbs + trunk)
- arthralgia/arthritis (64-100%)
- diffuse or tender lymphadenopathy
- hepatomegaly or splenomegaly
- dry cough
- cardiac failure

Investigations
- blood work: includes TSH and ESR; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

Differential Diagnosis
- diagnosis of exclusion
- rule out other disorders by history and physical exam

Treatment
- conservative
  - education
  - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
  - stress reduction, CBT
  - no evidence for alternative medicine such as biofeedback, meditation, acupuncture
- medical
  - low dose tricyclic antidepressant (e.g. amitriptyline)
    - for sleep restoration
  - select those with lower anticholinergic side effects
  - SNRI: duloxetine, milnacipran
  - anticonvulsant: pregabalin, gabapentin
  - analgesics may be beneficial for pain that interferes with sleep (NSAIDs, not narcotics)

Prognosis
- variable; usually chronic, unless diagnosed and treated early

Conclusions
- Moderate aerobic cardiorespiratory exercise improves function and well-being in patients with FM. Benefits from muscle strengthening and flexibility require additional research to delineate benefits.
Classification
- numerous classification systems proposed
- Yamaguchi’s criteria ([J Rheumatol 1992;19:424-30]): need 5 criteria to diagnose Still’s, at least 2 major
  - major criteria
    - T >39°C, intermittent, >1 wk
    - typical rash
    - WBC >10,000 (>80% granulocytes)
  - minor criteria
    - sore throat
    - lymphadenopathy ± splenomegaly
    - abnormal transaminases
    - negative ANA and RF
- exclusion criteria: infection, malignancy, rheumatic disease

Investigations
- ANA and RF negative
- markedly elevated ESR, CRP, ferritin (typically >1000 ng/mL, >2200 pmol/L)
  - total ferritin >5x ULN = 80% sensitive, 41% specific
- anemia, thrombocytosis, leucocytosis may occur
- transaminases, LDH may be elevated

Treatment
- refer to rheumatologist for treatment with biologics (anti-IL1 and anti-IL6 agents)
- begin management with low-dose glucocorticoids ± MTX

### Common Medications

#### Table 32. Common Medications for OA

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing (PO)</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
<td>acetaminophen</td>
<td>Tylenol®</td>
<td>500 mg tid q4h (4 g daily max)</td>
<td>1st line</td>
<td></td>
<td>Hepatotoxicity, Overdose Potentiates warfarin</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>ECASA</td>
<td>Entrophen®</td>
<td>325-975 mg qid</td>
<td>2nd line</td>
<td>GI bleed</td>
<td>Renal impairment, Allergy to ASA, NSAIDs, Pregnancy (T3)</td>
</tr>
<tr>
<td></td>
<td>ibuprofen</td>
<td>Advil®, Motrin®</td>
<td>200-600 mg tid</td>
<td></td>
<td></td>
<td>Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome</td>
</tr>
<tr>
<td></td>
<td>diclofenac</td>
<td>Voltaren®</td>
<td>125-500 mg bid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>diclofenac/misoprostol</td>
<td>Naprosyn®, Aleve®</td>
<td>7.5-15 mg OD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>naproxen</td>
<td>Mobicox®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>meloxicam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COX-2 INHIBITORS</td>
<td>celecoxib</td>
<td>Celebrex®</td>
<td>200 mg OD</td>
<td>High risk for GI bleed: age &gt;65 Hx of GI bleed, PUD</td>
<td>Renal impairment, Sufa allergy (celecoxib), Cardiovascular disease, Delayed ulcer healing</td>
<td>Renal/hepatic impairment, Rash</td>
</tr>
<tr>
<td>Other Treatments</td>
<td>Combination analgesics</td>
<td>Enhanced short-term effect compared to acetaminophen alone More adverse effects: sedation, constipation, nausea, GI upset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IA corticosteroid injection</td>
<td>Short-term (weeks-months) decrease in pain and improvement in function Used for management of an intraarticular inflammatory process when infection has been ruled out</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IA hyaluronic acid q6mo</td>
<td>Used for mild-moderate OA of the knees, however little supporting evidence, and not considered to be effective Precaution with chicken/egg allergy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Topical NSAIDs</td>
<td>1.5% wt/wt topical diclofenac (Pennsaid®) May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capsaicin cream</td>
<td>Mild decrease in pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucosamine sulfate ± chondroitin</td>
<td>Limited clinical studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 33. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COMMONLY USED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hydroxychloroquine</td>
<td>Plaquenil®</td>
<td>400 mg PO OD initially 200-400 mg PO OD maintenance (6.5 mg/kg ideal body weight per day)</td>
<td>Retinal disease, G6PD deficiency</td>
<td>GI symptoms, skin rash, macular damage, neuromyopathy Requires regular ophthalmological screening to monitor for retinopathy</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>Salazopyrin® Azulfidine® (US)</td>
<td>1000 mg PO bid-tid</td>
<td>Sulf/ASA allergy, kidney disease, G6PD deficiency</td>
<td>GI symptoms, rash, headache, leukopenia</td>
</tr>
<tr>
<td>methotrexate</td>
<td>Rheumatrex® Folex/Mexate®</td>
<td>7.5-25 mg PO/IM/SC qweekly</td>
<td>Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EIOH abuse</td>
<td>Oral ulcers, GI symptoms, cirrhosis, myelosuppression, pneumonitis, tubular necrosis</td>
</tr>
<tr>
<td>leflunomide</td>
<td>Arava®</td>
<td>10-20 mg PO OD</td>
<td>Liver disease</td>
<td>Alopecia, GI symptoms, liver dysfunction, pulmonary infiltrates</td>
</tr>
<tr>
<td><strong>NOT COMMONLY USED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cyclosporine</td>
<td>Neoral®</td>
<td>2.5-3 mg/kg/d divided and given in 2 doses PO</td>
<td>Kidney/liver disease, infection, HTN</td>
<td>HTN, decreased renal function, hair growth, tremors, bleeding</td>
</tr>
<tr>
<td>gold (injectable)</td>
<td>Solganal® Myocrysine®</td>
<td>50 mg IM q1wk after gradual introduction</td>
<td>IBD, kidney/liver disease</td>
<td>Rash, mouth soreness/ulcers, proteinuria, marrow suppression</td>
</tr>
<tr>
<td>azathioprine</td>
<td>Imuran®</td>
<td>2/5 mg/kg/d PO once daily</td>
<td>Kidney/liver disease TPMT deficiency</td>
<td>Rash, pancytopenia (especially ↓ WBC, ↑ AST, ALT), biliary stasis, vomiting, diarrhea</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>Cytoxan®</td>
<td>1 g/m²/mo IV as per protocol</td>
<td>Kidney/liver disease</td>
<td>Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEWER DMARDs (Biologics)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>etanercept</td>
<td>Enbrel®</td>
<td>25 mg biweekly or 50 mg weekly SC</td>
<td>Fusion protein of TNF receptor and Fc portion of IgG</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade®</td>
<td>3-5 mg/kg IV q8wk</td>
<td>Chimeric mouse/human monoclonal anti-TNF-α</td>
</tr>
<tr>
<td>adalimumab</td>
<td>Humira®</td>
<td>40 mg SC q2wk</td>
<td>Monoclonal anti-TNF-α</td>
</tr>
<tr>
<td>abatacept</td>
<td>Orencia®</td>
<td>IV infusion</td>
<td>Costimulation modulator of T-cell activation</td>
</tr>
<tr>
<td>rituximab</td>
<td>Rituxan®</td>
<td>2 IV infusions, 2 wk apart</td>
<td>Causes B-cell depletion, binds to CD20</td>
</tr>
<tr>
<td>certolizumab</td>
<td>Cimzia®</td>
<td>400 mg SC q2wk x3 then 200 mg SC q4wk</td>
<td>PEGylated monoclonal anti-TNF-α</td>
</tr>
<tr>
<td>golimumab</td>
<td>Simponi®</td>
<td>50 mg SC q month</td>
<td>Monoclonal anti-TNF-α</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>Actemra®</td>
<td>4-8 mg/kg IV q4wk</td>
<td>Interleukin-β receptor antagonist</td>
</tr>
</tbody>
</table>

**Risks of Biologics**
- Reactivation of TB or hepatitis B; patients require negative TB skin test, chest x-ray, and negative hepatitis B virus serology prior to starting any of these medications
- Increased risk of serious infections
- Worsening heart failure
**Landmark Rheumatology Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RHUMATOID ARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTEST</td>
<td><em>Ann Rheum Dis</em> 2008; 67:1086-103</td>
<td>Abatacept and infliximab have similar efficacy in RA patients who have failed MTX</td>
</tr>
<tr>
<td>ATTRACT</td>
<td><em>Lancet</em> 1999; 354:1932-9</td>
<td>Infliximab and MTX combined are more effective than MTX alone for patients with active RA</td>
</tr>
<tr>
<td>CIMESTRA</td>
<td><em>Arthritis Rheum</em> 2006; 54:1401-9</td>
<td>Combination of MTX and sulfasalazine is superior to either alone</td>
</tr>
<tr>
<td>COMET</td>
<td><em>Lancet</em> 2008; 372:375-82</td>
<td>Etanercept add-on therapy increases rates of remission in early RA</td>
</tr>
<tr>
<td>ERA</td>
<td><em>NEJM</em> 2000; 343:1586-93</td>
<td>Etanercept more rapidly decreases symptoms in early RA compared to MTX</td>
</tr>
<tr>
<td>European Leflunomide Study Group</td>
<td><em>Lancet</em> 1999; 353:259-66</td>
<td>Leflunomide is equal in efficacy to sulfasalazine</td>
</tr>
<tr>
<td>FIN-RACo</td>
<td><em>Lancet</em> 1999; 353:1568-73</td>
<td>Combination therapy with DMARDs improves remission rates in early RA</td>
</tr>
<tr>
<td>Infliximab and MTX</td>
<td><em>NEJM</em> 2000; 343:1594-602</td>
<td>Infliximab combined with MTX reduces joint damage in RA</td>
</tr>
<tr>
<td>Leflunomide RA Investigators Group</td>
<td><em>Arch Intern Med</em> 1999; 159:2542-50</td>
<td>Leflunomide is equivalent to MTX therapy and superior to placebo</td>
</tr>
<tr>
<td>PREMIER</td>
<td><em>Arthritis Rheum</em> 2006; 54:26-37</td>
<td>Combination therapy with adalimumab and MTX is superior to either alone in patients with early RA</td>
</tr>
<tr>
<td>Swefot</td>
<td><em>Lancet</em> 2009; 374:459-66</td>
<td>Anti-TNF agents are more effective second-line therapy than DMARDs in patients who fail MTX</td>
</tr>
<tr>
<td><strong>OSTEARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAIT</td>
<td><em>NEJM</em> 2006; 354:795-808</td>
<td>Glucosamine, chondroitin, and the combination of both are no more effective than placebo in treatment of knee OA</td>
</tr>
<tr>
<td><strong>LUPUS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belimumab</td>
<td><em>Lancet</em> 2011; 377:721-31</td>
<td>Treatment with belimumab reduces the incidence of BILAG A and B flares in patients with SLE compared to placebo</td>
</tr>
<tr>
<td>BILAG open-RCT</td>
<td><em>Rheumatology</em> 2010; 49:723-32</td>
<td>Low dose cyclosporine and azathioprine are equivalent in efficacy as maintenance therapy for SLE</td>
</tr>
<tr>
<td>Mycophenylate mofetil or intravenous cyclophosphamide</td>
<td><em>NEJM</em> 2005; 353:2219-28</td>
<td>Mycophenylate mofetil is more efficacious than cyclophosphamide in inducing remission of SLE nephritis</td>
</tr>
<tr>
<td><strong>CONNECTIVE TISSUE DISEASES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine or MTX maintenance for ANCA-associated vasculitis</td>
<td><em>NEJM</em> 2008; 359:2790-803</td>
<td>MTX and azathioprine are equally safe and effective as maintenance agents in ANCA vasculitis</td>
</tr>
<tr>
<td>Cyclophosphamide in scleroderma lung disease</td>
<td><em>NEJM</em> 2006; 354:2655-66</td>
<td>Cyclophosphamide therapy leads to transient improvements in lung function, skin scores, and overall health in patients with scleroderma</td>
</tr>
<tr>
<td>Etanercept plus standard therapy for granulomatosis with polyangiitis</td>
<td><em>NEJM</em> 2005; 352:351-61</td>
<td>Etanercept is not effective in inducing remission in patients with ANCA vasculitis</td>
</tr>
<tr>
<td>Mycophenylate mofetil vs. azathioprine for maintenance in ANCA-associated vasculitis</td>
<td><em>JAMA</em> 2010; 304:2381-8</td>
<td>Mycophenylate mofetil is less effective than azathioprine for maintaining disease in ANCA-associated vasculitis</td>
</tr>
<tr>
<td>Rituximab vs. cyclophosphamide for ANCA-associated vasculitis</td>
<td><em>NEJM</em> 2010; 363:221-32</td>
<td>Rituximab is not inferior to cyclophosphamide for induction of remission in ANCA vasculitis</td>
</tr>
<tr>
<td><strong>GOUT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febuxostat vs. allopurinol</td>
<td><em>NEJM</em> 2005; 353:2450-61</td>
<td>Febuxostat is more effective than allopurinol at lowering serum urate, and has similar effectiveness on flare reduction</td>
</tr>
</tbody>
</table>
References

Kirkhoff A. Diagnosis and management of inflammatory polyarthritis. CMAJ 2000;162:1635-1638.
Shuja K. What laboratory tests are needed? CMAJ 2000;162:1170-1183.
Wards JP. Osteoporosis. CMAJ 2001;165:45-50.
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Penis Anatomy
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Figure 1. Midline cross-section of abdominal wall

Figure 2. Anatomy of scrotum

Figure 3. Essential genitourinary tract male anatomy

• recall that the anatomical position of the penis is erect; therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis
Urologic History

- follow the OPQRSTUVW approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
- inquire about risk factors: past urologic disease (e.g. UTI, stones, STD, cancers, anatomic abnormalities, family Hx, medications, lifestyle factors, trauma, previous surgical procedures)
- urinary habits
  - frequency of voiding, quality of urine, volume of voids, incontinence, nocturia
  - specific urinary symptoms include
    - storage symptoms: frequency, nocturia, urgency
    - voiding symptoms: straining, hesitancy, dysuria, intermittency, post-void dribbling, reduced stream, feeling of incomplete voiding
    - hematuria: part of stream during which bleeding occurs, blood clots
    - incontinence: rushing to washroom (urge); leakage with coughing, sneezing, laughing (stress); constant dribbling (overflow)
- sexual function
  - scrotal mass: see Scrotal Mass, U28
  - ED: see Erectile Dysfunction, U30
  - infertility: see Infertility, U33
- risk factors
  - past urologic disease (e.g. UTI, stones, cancers, STD), anatomic abnormalities, trauma, previous surgical procedures, medications, family Hx, lifestyle factors
- associated symptoms
  - N/V
  - bowel dysfunction
- constitutional symptoms
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant vascular disease. If there is new onset ED, consider screening for diabetes and CAD risk factors.
Hematuria (Blood in the Urine)

Macroscopic (Gross) Hematuria

Definition
• blood in the urine that can be seen with the naked eye

Classification
• see Nephrology, NP21

Etiology

Table 1. Etiology by Age Group

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20</td>
<td>UTI, glomerulonephritis, congenital abnormalities</td>
</tr>
<tr>
<td>20-40</td>
<td>UTI, stones, bladder tumor</td>
</tr>
<tr>
<td>40-60</td>
<td>Male: bladder tumor, stones, UTI</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Male: BPH, bladder tumor, UTI, RCC</td>
</tr>
<tr>
<td></td>
<td>Female: UTI, stones, bladder tumor</td>
</tr>
</tbody>
</table>

Table 2. Etiology by Type

<table>
<thead>
<tr>
<th>Pseudohematuria</th>
<th>Infectious/Inflammatory</th>
<th>Malignancy</th>
<th>Benign</th>
<th>Structural</th>
<th>Hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal bleeding</td>
<td>Pyelonephritis</td>
<td>RCC (mainly in adult population)</td>
<td>BPH Polyps Exercise-induced</td>
<td>Stones</td>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Dyes (beets, rhodamine B in candy and juices)</td>
<td>Cystitis</td>
<td>UCC</td>
<td></td>
<td>Trauma</td>
<td>Coagulation defects</td>
</tr>
<tr>
<td>Hemoglobin (hemolytic anemia)</td>
<td>Urethritis</td>
<td>Wilms’ tumor (mainly in pediatric population)</td>
<td></td>
<td>Foreign body</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Myoglobin (rhabdomyolysis)</td>
<td>Glomerulonephritis</td>
<td>Leukemia</td>
<td></td>
<td>Urethral structure</td>
<td>Thromboembolism</td>
</tr>
<tr>
<td>Drugs (rifampin, phenazopyridine, phenytoin)</td>
<td>Tuberculosis</td>
<td></td>
<td></td>
<td>Poly cystic kidneys</td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
<td></td>
<td></td>
<td>Arteriovenous malformation</td>
<td></td>
</tr>
<tr>
<td>Luxatives (phenolphthalein)</td>
<td></td>
<td></td>
<td></td>
<td>Infract</td>
<td></td>
</tr>
</tbody>
</table>

History
• inquire about timing of hematuria in urinary stream
  • initial: anterior urethra
  • terminal: bladder neck and prostatic urethra
  • total: bladder and/or above

Investigations
• CBC (r/o anemia, leukocytosis), electrolytes, Cr, BUN, INR, PTT
• urine studies
  • U/A, C&S, cytology
• imaging
  • CT (with contrast) has largely replaced IVP to investigate upper tracts
    • consider contraindications to contrast; allergy, renal insufficiency
    • U/S alone is not sufficient
  • cystoscopy to investigate lower tract (possible retrograde pyelogram)

Acute Management of Severe Bladder Hemorrhage
• manual irrigation via catheter with normal saline to remove clots
• CBI using large (22-26 Fr) 3-way Foley to help prevent clot formation
• cystoscopy if active bleeding
  • identify resectable tumors
  • coagulate obvious sites of bleeding
• refractory bleeding
  • intravesical agents
    • continuous intravesical irrigation with 1% aluminum potassium sulfate solution as needed
    • intravesical instillation of 1% silver nitrate solution
    • intravesical instillation of 1-4% formalin (requires GA and pre-procedure cystogram to rule out reflux)
  • embolization or ligation of iliac arteries
  • cystectomy and diversion (rarely performed)
Microscopic Hematuria

Definition
- blood in the urine that is not visible to the naked eye
- >3 RBCs/HPF on urinalysis of at least two separate samples

Figure 6. Workup of asymptomatic microscopic hematuria
Based on CUA Guidelines. Alternatively, the AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative workup is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists

Voiding Dysfunction
- see Gynecology, GY34 for relevant female topics

Voiding
- two phases of lower urinary tract function
  1. storage phase (bladder filling and urine storage)
     • accommodation and compliance
     • no involuntary contraction
  2. voiding phase (bladder emptying)
     • coordinated detrusor contraction
     • synchronous relaxation of outlet sphincters
     • no anatomic obstruction
- voiding dysfunction can therefore be classified as
  • failure to store: due to bladder or outlet
  • failure to void: due to bladder or outlet
- three types of symptoms
  • storage (formerly known as irritative)
  • voiding (formerly known as obstructive)
  • post-voiding

Urinary Incontinence

Definition
- involuntary leakage of urine

Etiology
- urgency incontinence
  • detrusor overactivity
  • CNS lesion, inflammation/infection (cystitis, stone, tumor), bladder neck obstruction (tumor, stone), BPH, idiopathic
• decreased compliance of bladder wall (inability to store urine)
  • CNS lesion, fibrosis
  • sphincter/urethral problem
• stress urinary incontinence (SUI)
  • common in women; seen in men after prostate cancer treatment or pelvic operations
  • urethral hypermobility
  • weakened pelvic floor and musculofascial urethral and vaginal supporting mechanisms
    allows bladder neck and urethra to descend with increased intra-abdominal pressure
  • urethra is pulled open by greater motion of posterior wall of outlet relative to anterior wall
  • associated with childbirth, pelvic surgery, aging, levator muscle weakness, obesity
• intrinsic sphincter deficiency (ISD): weakness of the urethra and associated smooth and striated muscle elements
  • pelvic surgery, neurologic problem, aging and hypoestrogen state
  • ISD and urethral hypermobility can co-exist
• mixed incontinence
  • combination of stress and urgency incontinence
• overflow incontinence
  • is a term sometimes used to describe urinary incontinence as a complication of urinary retention; for causes of urinary retention see Table 4
  • use of the term is used it should be accompanied by the associated pathophysiology (e.g. BPH with overflow incontinence)

Epidemiology
• variable prevalence in women: 25-45%
• F:M = 2:1
• more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

Table 3. Urinary Incontinence: Types and Treatments

<table>
<thead>
<tr>
<th>Type</th>
<th>Urgency</th>
<th>Stress</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Involutionary leakage of urine preceded by a strong, sudden urge to void</td>
<td>Involutionary leakage of urine with sudden increases in intra-abdominal pressure</td>
<td>Urinary leakage associated with urgency and increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Etiology</td>
<td>Bladder (detrusor overactivity)</td>
<td>Urethra/sphincter weakness, post-partum pelvic musculature weakness</td>
<td>Combination of bladder and sphincter issues</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hx</td>
<td>Urodynamics</td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td>Lifestyle changes (fluid alterations, diet, etc.) Bladder habit training Anticholinergics (3 agonist Neumodulation Botulinum toxin A</td>
<td>Weight loss Kegel exercises Bulking agents Surgery (sling, tension-free vaginal tape, transobturator tape, artificial sphincters)</td>
<td>Combination of management of urge and stress incontinence</td>
</tr>
</tbody>
</table>

Urinary Retention

Table 4. Etiology of Urinary Retention

<table>
<thead>
<tr>
<th>Outflow Obstruction</th>
<th>Bladder Innervation</th>
<th>Pharmacologic</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder neck or urethra: calculi, clot, foreign body, neoplasm, neurologic (DSD)</td>
<td>Intracranial: CVA, tumor, Parkinson’s, cerebral palsy</td>
<td>Anticholinergics</td>
<td>GU: UTI, prostatitis, abscess, genitourinary herpes</td>
</tr>
<tr>
<td>Prostate: BPH, prostate cancer</td>
<td>Spinal cord: injury, disc herniation, MS</td>
<td>Antihypertensives (ganglionic blockers, methyldopa)</td>
<td>Infected foreign body</td>
</tr>
<tr>
<td>Urethra: stricture, phimosis, traumatic disruption</td>
<td>DM</td>
<td>OTX cold medications containing ephedrine or pseudoephedrine</td>
<td>Varicella zoster</td>
</tr>
<tr>
<td>Miscellaneous: constipation, pelvic mass</td>
<td>Post-abdominal or pelvic surgery</td>
<td>Antihistamines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psychosomatic substances (e.g. eczema)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
• suprapubic pain
• palpable and/or percussible bladder (suprapubic)
• possible purulent/bloody meatal D/C
• increased size of prostate or reduced anal sphincter tone on DRE
• neurological: presence of abnormal or absent deep tendon reflexes, reduced "anal wink", saddle anesthesia
**Investigations**
- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

**Treatment**
- treat underlying cause
- catheterization
  - acute retention
    - immediate catheterization to relieve retention; leave Foley in to drain bladder; follow-up to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - intermittent catheterization by patient may be used; definitive treatment depends on etiology
- suprapubic tube placement
- for post-operative patients with retention:
  - encourage ambulation
  - α-blockers to relax bladder neck outlet
  - may need catheterization
  - definitive treatment will depend on etiology

**Benign Prostatic Hyperplasia**

**Definition**
- periurethral hyperplasia of stroma and epithelium in prostatic transition zone
- prostatic smooth muscle cells play a role in addition to hyperplasia

**Etiology**
- etiology unknown
  - DHT required (converted from testosterone by 5-α reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors
  - genetic: increased risk in 1st degree relatives and twin studies

**Epidemiology**
- age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
- 25% of men will require treatment

**Clinical Features**
- result from outlet obstruction and compensatory changes in detrusor function
- voiding and storage symptoms
- DRE
  - prostate is smooth, rubbery, and symmetrically enlarged
- complications
  - retention
  - overflow incontinence
  - hydronephrosis
  - renal insufficiency
  - infection
  - gross hematuria
  - bladder stones

**Investigations**
- Hx, assessing LUTS and impact on QOL
  - may include self-administered questionnaires (IPSS or AUA symptom index for severity, progression, and treatment response)
- P/E, including DRE
- U/A to exclude UTI
- Cr to assess renal function
- uroflowmetry to measure flow rate (optional)
- PVR (optional)
- consider cystoscopy or transrectal ultrasound prior to potential surgical management to evaluate outlet and prostate volume
- biopsy if suspicious for malignancy, i.e. elevated PSA or abnormal DRE

**Figure 7. Cross-section of prostate**

- Prostate size does not correlate well with symptoms in BPH
- Approximate Prostate Sizes
  - 20 cc – chestnut
  - 25 cc – plum
  - 50 cc – lemon
  - 75 cc – orange
  - 100 cc – grapefruit

**AUA BPH Symptom Score**

- FUNWISE
  - Frequency
  - Urgency
  - Nocturia
  - Weak stream
  - Intermittency
  - Straining
  - Emptying, incomplete feeling of
  - Each symptom graded out of 5
  - 0-7: Mildly symptomatic
  - 8-19: Moderately symptomatic
  - 20-35: Severely symptomatic
  - Note: dysuria not included in score but is commonly associated with BPH
Urethral Stricture

Definition
- decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

Etiology
- congenital
  - failure of normal canalization (i.e. posterior urethral valves)
- trauma
  - instrumentation/catheterization (most common)
  - external trauma (e.g. burns, straddle injury)
  - foreign body
  - infection
  - long-term indwelling catheter
  - STD (gonococcal or chlamydial disease)
- inflammation
  - balanitis xerotica obliterans (BXO; lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal and urethral stenosis

Clinical Features
- voiding symptoms
- urinary retention
- hydrourephrosis
- related infections: recurrent UTI, secondary prostatitis/epididymitis

Investigations
- laboratory findings
  - flow rates <10 mL/s (normal ~20 mL/s) on uroflowmetry
  - urine culture usually negative, but U/A may show pyuria
- radiologic findings
  - RUG and VCUG will demonstrate location
- cystoscopy

Treatment
- urethral dilatation
  - temporarily increases lumen size by breaking up scar tissue
  - healing will often reform scar tissue, recurrence of stricture
- visual internal urethrotomy (VIU)
  - endoscopically incise stricture
  - equal success rates to dilation with mid bulbar strictures <2 cm
  - high rate of recurrence (30–80%), avoid in younger patients
- open surgical reconstruction
  - complete stricture excision with anastomosis, ± urethroplasty depending on location and size of stricture
Neurogenic Bladder

Definition
• malfunctioning urinary bladder due to deficiency in some aspect of its innervation

Neurophysiology

Table 6. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply

<table>
<thead>
<tr>
<th>Nerve Fibers</th>
<th>Nerve Roots</th>
<th>Neurotransmitter/Receptor</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic</td>
<td>T10-L2</td>
<td>NA/Adrenergic</td>
<td>Trigone, internal sphincter, proximal urethra (α) Bladder body (β)</td>
</tr>
<tr>
<td>Somatic (pudendal)</td>
<td>S2-4</td>
<td>ACh/Nicotinic</td>
<td>External sphincter</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>S2-4</td>
<td>ACh/Muscarinic (M2, M3)</td>
<td>Detrusor</td>
</tr>
</tbody>
</table>

• stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  ▪ micturition
    ▪ stimulation of parasympathetic neurons (bladder contraction)
    ▪ inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  ▪ urine storage
    ▪ opposite of micturition
  ▪ voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
  ▪ cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem

Classification of Neurologic Voiding Dysfunction
• neuropathic detrusor overactivity (formerly termed detrusor hyperreflexia)
  ▪ lesion above PMC (e.g. stroke, tumor, MS, Parkinson’s disease)
  ▪ loss of voluntary inhibition of voiding
  ▪ intact pathway inferior to PMC maintains coordination of bladder and sphincter
• detrusor sphincter dyssynergia (DSD)
  ▪ suprasacral lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  ▪ loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
  ▪ component of detrusor overactivity as well
• detrusor atony/areflexia
  ▪ lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality, post abdominoperineal resection)
  ▪ flaccid bladder which fails to contract
  ▪ may progress to poorly compliant bladder with high pressures
• peripheral autonomic neuropathy
  ▪ deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
• muscular lesion
  ▪ can involve detrusor, smooth/striated sphincter

Neuro-Urologic Evaluation
• hx and P/E (urologic and general neurologic)
• U/A, renal profile
• imaging
  ▪ U/S to r/o hydronephrosis and stones
• cystoscopy
• urodynamic studies
  ▪ uroflowmetry to assess flow rate, pattern
  ▪ filling CMG to assess capacity, compliance, detrusor overactivity
  ▪ voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outflow obstruction
  ▪ video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
• EMG ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

Treatment
• goals of treatment
  ▪ prevent renal failure
  ▪ prevent infections
  ▪ achieve social continence
• clean intermittent catheterization (CIC)
• treatment options depend on status of bladder and urethra
  - bladder hyperactivity → anticholinergic medications to relax bladder (see *Urinary Incontinence, U5*)
    • if refractory
      – botulinum toxin injections into bladder wall
      – occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      – occasionally urinary diversion (ileal conduit or continent diversion) in severe cases if bladder management unsuccessful
  - flaccid bladder → CIC

**Dysuria**

**Definition**
• painful urination

**Etiology**

| Table 7. Differential Diagnosis of Dysuria |
|-----------------|---------------------------------|
| **Infectious**  | Cystitis, urethritis, prostatitis, epididymitis/orchitis (if associated with lower tract inflammation), cervicitis, vulvovaginitis, perineal inflammation/infection, TB, vestibulitis |
| **Neoplasm**    | Kidney, bladder, prostate, penis, vagina/vulva, BPH |
| **Calci**       | Bladder stone, urethral stone, ureteral stone |
| **Inflammatory**| Seronegative arthropathies (reactive arthritis: arthritis, uveitis, urethritis), drug side effects, autoimmune disorders, chronic pelvic pain syndrome (CPPS), interstitial cystitis |
| **Hormonal**    | Endometriosis, hypoestrogenism |
| **Trauma**      | Catheter insertion, post-coital cystitis (honeymoon cystitis) |
| **Psychogenic** | Somatization disorder, depression, stress/anxiety disorder |
| **Other**       | Contact sensitivity, foreign body, radiation/chemical cystitis, diverticulum |

**Investigations**
• focused Hx and P/E to determine cause (fever, d/c, conjunctivitis, CVA tenderness, back/joint pain)
  - any d/c (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal d/c
  - U/A and urine C&S
  - if suspect infection, may start empiric Antibiotic treatment
  - ± imaging of urinary tract (tumor, stones)

**Hydronephrosis**

**Definition**
• dilation of the renal pelvis and calyces caused by the impairment in antegrade urine flow

**Etiology**
• mechanical
  - congenital: see *Congenital Abnormalities, U35*
  - acquired
    • intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral stricture, phimosis, previous urological surgery
    • extrinsic: trauma, neoplasms (uterine fibroid; colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
• functional
  - neuropathic: neurogenic bladder, diabetic neuropathy, spinal cord disease
  - pharmacologic: anticholinergics, α-adrenergic agonists
  - hormonal: pregnancy (progesterone decreases ureteral tone)

**Investigations**
• focused Hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, Hx of UTIs, calculi, and PID and urological surgery
• CBC, electrolytes, Cr, BUN, U/A, C&S
• imaging studies (U/S is >90% sensitive and specific)
  ▪ MAG3 diuretic renogram: evaluates differential renal function and demonstrates if functional obstruction exists

Treatment
• hydronephrosis can be physiologic
• treatment should be guided at improving symptoms, treating infections, or improving renal function
• urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure

Post-Obstructive Diuresis

Definition
• polyuria resulting from relief of severe chronic obstruction
• >3 L/24 h or >200 cc/h over each of two consecutive hours

Pathophysiology
• physiologic POD secondary to excretion of retained urea, Na⁺, and H₂O (high osmotic load) after relief of obstruction
  ▪ self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
• pathologic POD is a Na⁺-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to
  ▪ decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  ▪ increased medullary blood flow (solute washout)
  ▪ increased flow and solute concentration in the distal nephrons

Management
• admit patient and closely monitor hemodynamic status and electrolytes (Na⁺ and K⁺ q6-12h and replace prn; follow Cr and BUN to baseline)
• monitor U/O q2h and ensure total fluid intake <U/O by replacing every 1 cc U/O with 0.5 cc 1/2 NS IV (PO fluids if physiologic POD)
• avoid glucose-containing fluid replacement (iatrogenic diuresis)

Table 8. Antibiotic Treatment of Urological Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urethritis</strong></td>
<td>Non-Gonococcal:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>azithromycin (1 g PO)</td>
<td>x 1</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>doxycycline (100 mg PO bid)</td>
<td>7 d</td>
</tr>
<tr>
<td></td>
<td>Gonococcal:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone (250 mg IM) ANND treat for Chlamydia trachomatis</td>
<td>x 1</td>
</tr>
<tr>
<td><strong>Simple, Uncomplicated UTI</strong></td>
<td>TMP-SMX (160 mg/800 mg PO bid)</td>
<td>3 d</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nitrofurantoin (100 mg PO bid)</td>
<td>5 d</td>
</tr>
<tr>
<td><strong>Complicated UTI</strong> (see Classification, U12 for features)</td>
<td>ciprofloxacin (1 g PO daily OR 400 mg IV q12h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ampicillin (1 g IV q6h) + gentamicin (1 mg/kg IV q8h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone (1-2 g IV q24h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td><strong>Recurrent/Chronic Cystitis</strong></td>
<td>*prophylactic treatment continuous: TMP-SMX (40 mg/200 mg PO qd OR 3x/wk)</td>
<td>6-12 mo</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nitrofurantoin (50-100 mg PO qd)</td>
<td>6-12 mo</td>
</tr>
<tr>
<td></td>
<td>post-coital: TMP-SMX (40 mg/200 mg-80 mg/400 mg)</td>
<td>within 2 h of coitus</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nitrofurantoin (50-100 mg PO qd)</td>
<td>within 2 h of coitus</td>
</tr>
</tbody>
</table>
Table 8. Antibiotic Treatment of Urological Infections (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Prostatitis</td>
<td>ciprofloxacin (500-750 mg PO bid) OR TMP-SMX (160 mg/800 mg PO bid) OR IV therapy with gentamicin and ampicillin, penicillin with β-lactamase inhibitor, 3rd gen cephalosporin, OR a fluoroquinolone</td>
<td>2-4 wk OR 4 wk OR 4 wk total (IV and oral step-down)</td>
</tr>
<tr>
<td>Chronic Prostatitis</td>
<td>ciprofloxacin (500 mg PO bid)</td>
<td>4-6 wk</td>
</tr>
<tr>
<td>Epididymitis/Orchitis</td>
<td>ceftriaxone (200 mg IM) AND doxycycline (100 mg PO bid) OR ofloxacin (300 mg PO bid)</td>
<td>≤35 yr: x 1 OR ≥35 yr: 10 d</td>
</tr>
<tr>
<td>Acute Uncomplicated Pyelonephritis</td>
<td>ciprofloxacin (500 mg PO bid) ± ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV) OR IV therapy with a fluoroquinolone, gentamicin and ampicillin, extended spectrum cephalosporin, extended spectrum penicillin, OR a carbapenem</td>
<td>Acute uncomplicated pyelonephritis: suspected or confirmed enterococcus infection requires treatment with ampicillin</td>
</tr>
</tbody>
</table>

Urinary Tract Infection

- for UTIs during pregnancy, see Obstetrics, OB19

Definition
- symptoms suggestive of UTI + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy)

Classification
- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, male patients, immunocompromised, diabetic, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see Recurrent/Chronic Cystitis, U13

Risk Factors
- stasis and obstruction
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder
- foreign body
  - introduce pathogen or act as nidus of infection e.g. catheter, instrumentation
- decreased resistance to organisms
  - DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors
  - trauma, anatomic abnormalities, female, sexual activity, fecal incontinence

Clinical Features
- storage symptoms: frequency, urgency, dysuria
- voiding symptoms: hesitancy, post-void dribbling
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

Organisms
- typical organisms
- atypical organisms
  - tuberculosis (TB)
  - *Chlamydia trachomatis*
  - *Mycoplasma (Ureaplasma urealyticum)*
  - fungi (*Candida*)

Indications for Investigations
- pyelonephritis
- persistence of pyuria/symptoms following adequate antibiotic therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- hx of structural abnormalities/decreased flow
**Investigations**
- U/A, urine C&S
  - UA: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see *Microscopic Hematuria, U5*)
- U/S, CT scan if indicated

**Treatment**
- see Table 8 for approach to ABx therapy
- if febrile, consider admission with IV therapy and r/o obstruction

**Recurrent/Chronic Cystitis**

**Definition**
- ≥3 UTIs/yr

**Etiology**
- bacterial reinfection (80%) vs. bacterial persistence (relapse)
  - *bacterial reinfection*
    - recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  - *bacterial persistence*
    - same organism cultured within 2 wk of sensitivity-based therapy

**Investigations**
- assess predisposing factors as described above
- investigations may include cystoscopy, U/S, CT

**Treatment**
- lifestyle changes (limit caffeine intake, increase fluid/H2O intake)
- ABx: continuous vs. post-coital
- post-menopausal women: consider topical or systemic estrogen therapy
- no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

**Interstitial Cystitis**
(Painful Bladder or Bladder Pain Syndrome)

**Definition**
- bladder pain, chronic urgency and frequency without other reasonable causation

**Classification**
- non-ulcerative (more common)
- ulcerative

**Etiology**
- unknown
  - theories: increased epithelial permeability, autoimmune, neurogenic, defective GAG layer overlying mucosa
  - associations: severe allergies, IBS, fibromyalgia

**Epidemiology**
- prevalence: 20/100,000
- 90% of cases are in females
- mean age at onset is 40 yr (non-ulcerative tends to affect a younger to middle-aged population, while ulcerative tends to be seen in middle-aged to older)

**Clinical Features**
- pain associated with the bladder
- glomerulations (submucosal petechiae) or Hunner’s lesions (ulcers) on cystoscopic examination
- urinary urgency
- negative U/A, urine C&S, and urine cytology

**Differential Diagnosis**
- UTI, vaginitis, bladder tumor
- radiation/chemical cystitis
- eosinophilic/TB cystitis
- bladder calculi
Treatment
- first-line: patient empowerment (diet, lifestyle, stress management), pain management
- second-line
  - oral: pentosan polysulfate sodium, amitriptyline, cimetidine, hydroxyzine
  - intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine
- third-line: cystoscopy with bladder hydrodistension (traditionally diagnostic) under GA, treat Hunner's lesions if present
- fourth-line: neuromodulation, pain management
- fifth-line: cyclosporine A, intradetrusor BTX
- sixth-line: diversion w/ or w/out cystectomy, substitution cystoplasty
- surgery (last resort): augmentation cystoplasty, or urinary diversion ± cystectomy

Acute Pyelonephritis

Definition
- infection of the renal parenchyma with local and systemic manifestations
- clinical diagnosis of flank pain, fever and elevated WBC

Etiology
- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
- causative microorganisms
  - gram positives: Enterococcus faecalis, S. aureus, S. saprophyticus
  - gram negatives: E. coli (most common), Klebsiella, Proteus, Pseudomonas, Enterobacter
- common underlying causes of pyelonephritis
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

Clinical Features
- rapid onset (<24 h)
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness or exquisite flank pain

Investigations
- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging indicated if suspicious of complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

Treatment
- hemodynamically stable
  - outpatient oral ABx treatment ± single initial IV dose (see Table 8)
- severe or non-resolving
  - admit, hydrate, and treat with IV ABx (see Table 8)
- emphysematous pyelonephritis
  - percutaneous nephrostomy tube and antibiotics first line
- consider early nephrectomy after IV ABx started and patient stabilized
- renal obstruction
  - admit for emergent stenting or percutaneous nephrostomy tube

Prostatitis/Prostatodynia

Epidemiology
- most common urologic diagnosis in men <50 yr
- prevalence 2-12%

Nitrofurantoin has poor tissue penetration and therefore is not used to treat pyelonephritis (requires post-renal uroconcentration)

Four Symptom Scores Exist to Evaluate and Monitor Patients with Interstitial Cystitis
- Interstitial Cystitis Symptom Index (ICSI)
- Interstitial Cystitis Problem Index (ICPI)
- Wisconsin Interstitial Cystitis (UW-IC) Scale
- Pain, Urgency and Frequency (PUF) Score

4-Glass Test: Prostatic source is suggested when colony counts in EPS and VB3 exceed those of VB1 and VB2 by 10x

Prostatic massage may cause extreme tenderness and increased risk of inducing sepsis, abscess, or epididymo-orchitis

It is not recommended to do a serum PSA during acute bacterial prostatitis
Classification

Table 9. Comparison of the Three Types of Prostatitis

<table>
<thead>
<tr>
<th>Category I: Acute Bacterial Prostatitis</th>
<th>Category II: Chronic Bacterial Prostatitis</th>
<th>Category III: Chronic Pelvic Pain Syndrome (CPPS) (Abacterial)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Recurrent exacerbations of acute prostatitis-like signs and symptoms</td>
<td>Divided into inflammatory (IIIA) and non-inflammatory (IIIB)</td>
</tr>
<tr>
<td>Ascending urethral infection with KEEPS (see U12 sidebar): 80% E. coli (often associated with outlet obstruction, recent cystoscopy, prostatic biopsy) Most infections occur in the peripheral zone (see Figure 7, U7)</td>
<td>Recurrent UTI with same organism</td>
<td>Intraprostatic reflux of urine ± urethral hypertonia</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>Pelvic pain, storage LUTS, ejaculatory pain, post- ejaculatory pain</td>
<td>Pelvic pain, storage LUTS, ejaculatory pain, post- ejaculatory pain</td>
</tr>
<tr>
<td>Acute onset fever, chills, malaise Rectal, lower back, and perineal pain LUTS</td>
<td><strong>Investigations</strong></td>
<td>Same as per Category II</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>ABx (see Table 8)</td>
<td>Supportive measures</td>
</tr>
<tr>
<td>Supportive measures PO or IV ABx depending how sick (see Table 8) May consider catheterization in patients with severe obstructive LUTS or retention I&amp;D of abscess if present</td>
<td>Consider addition of an α-blocker</td>
<td>Trail of ABx therapy if newly diagnosed</td>
</tr>
</tbody>
</table>

*NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index

Epididymitis and Orchitis

**Etiology**
- common infectious causes
  - <35 yr: N. gonorrhoeae or Chlamydia trachomatis
  - ≥35 yr or penetrative anal intercourse: GI organisms (especially E. coli)
- other causes
  - mumps infection may involve orchitis, post-parotitis
  - TB
  - syphilis
  - granulomatous (autoimmune) in elderly men
  - amiodarone (involves only head of epididymis)
  - chemical: reflux of urine into ejaculatory ducts

**Risk Factors**
- UTI
- unprotected sexual contact
- instrumentation/catheterization
- increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis
- immunocompromise

**Clinical Features**
- sudden onset scrotal pain and swelling ± radiation along cord to flank
- scrotal erythema and tenderness
- fever
- storage symptoms, purulent d/c
- reactive hydrocele

**Investigations**
- U/A, urine C&S
- urethral d/c: Gram stain/culture
- if diagnosis uncertain, must do
  - color-flow Doppler U/S to r/o testicular torsion

**Treatment**
- r/o torsion (see Investigations and Table 23, U28)
- see Table 8 for ABx therapy
- scrotal support, bed rest, ice, analgesia

**Complications**
- if severe → testicular atrophy
- 30% have persistent infertility problems

Prehn’s Sign: pain may be relieved with elevation of testicles in epididymitis but not in testicular torsion. Poor sensitivity, especially in children

If unsure between diagnoses of epididymitis and torsion, always go to OR
Remember: torsion >6 h has poor prognosis

Inadequately treated acute epididymitis may lead to chronic epididymitis or epididymo-orchitis
U16  Urology  Infectious and Inflammatory Diseases/Stone Disease  Essential Med Notes 2015

Urethritis

Etiology
• infectious or inflammatory (e.g. reactive arthritis)

Table 10. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

<table>
<thead>
<tr>
<th>Causative Organism</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Hx of sexual contact, thick, profuse, yellow-gray purulent d/c, ± urinalysis</td>
<td>see Table 8</td>
</tr>
<tr>
<td></td>
<td>Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen</td>
<td></td>
</tr>
<tr>
<td>Chlamydia trachomatis</td>
<td>Hx of sexual contact, mucoid whitish purulent d/c, ± storage LUTS</td>
<td>see Table 8</td>
</tr>
<tr>
<td></td>
<td>Gram stain demonstrates &gt;4 PMN/oil immersion field, no evidence of N. gonorrhoeae, urine PCR and/or culture from urethral specimen</td>
<td></td>
</tr>
</tbody>
</table>

Stone Disease

Epidemiology
• prevalence of 2-3%
• M:F = 3:1
• peak incidence 30-50 yr of age
• recurrence rate: 10% at one yr, 50% at 5 yr, 60-80% lifetime

Risk Factors
• hereditary: RTA, Glucose-6-phosphate dehydrogenase deficiency, cystinuria, xanthinuria, oxaluria, etc.
• lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
• medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, and zonisamide
• medical conditions: UTI (with urea-splitting organisms: Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus), myelolipolytic disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumor lysis syndrome, sarcoidosis, histoplamosis), obesity (BMI >30)

Clinical Features
• urinary obstruction → upstream distention → pain
  • flank pain from renal capsular distention (non-colicky)
  • severe wakening and waning pain radiating from flank to groin, testis, or tip of penis due to stretching of collecting system or ureter (ureteral colic)
  • writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
  • occasionally symptoms of trigonal irritation (frequency, urgency)
  • bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
  • if fever, r/o concurrent pyelonephritis and/or obstruction

Table 11. Differential Diagnosis of Renal Colic

<table>
<thead>
<tr>
<th>GU</th>
<th>Abdominal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis</td>
<td>AAA</td>
<td>Radiculitis (L1): herpes zoster, nerve root compression</td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>Bowel ischemia</td>
<td></td>
</tr>
<tr>
<td>from other cause: UPJ</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>obstruction, clot colic secondary to gross hematuria, sloughed papilae</td>
<td>Other acute abdominal crisis</td>
<td></td>
</tr>
<tr>
<td>Gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, PID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Location of Stones
• calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
• pelvis: tend to cause obstruction at UPJ, may cause persistent infection
• ureter: <5 mm diameter will pass spontaneously in 75% of patients

Stone Pathogenesis
• supersaturation of stone constituents (at appropriate temperature and pH)
• stasis, low flow, and low volume of urine (dehydration)
• crystal formation and stone nidus
• loss of inhibitory factors
  • citrate (forms soluble complex with calcium)
  • magnesium (forms soluble complex with oxalate)
  • pyrophosphate
  • Tamm-Horsfall glycoprotein

If culture negative or unresponsive to treatment consider: Ureaplasma urealyticum, Mycoplasma genitalium, Trichomonas vaginalis, HSV, or adenovirus

Reactive Arthritis (formerly known as Reiter’s syndrome)
Urethritis, uveitis (or conjunctivitis), and arthitis (can’t pee, can’t see, can’t climb a tree)

Key Points in Stone Hx
• Diet (especially FLUID INTAKE)
• Predisposing medical conditions
• Predisposing medications
• Previous episodes/investigations/treatments
• Family Hx (1st degree relative)

The four narrowest passage points for upper tract stones are:
• UPJ
• Pelvic brim
• Under vas deferens/broad ligament
• UVJ

Radiopaque  Radiolucent
KUB  Calcium  Urac acid
Struvite  Indinavir
Cystine  Atazanavir
CT  Calcium  Indinavir
Struvite  Atazanavir
Cystine  Indinavir
Urac acid  Atazanavir
**Approach to Renal Stone**

**Investigations**

*Figure 8. Approach to renal stone*

**Table 12. Investigations for Renal Stones**

<table>
<thead>
<tr>
<th>CBC, uric acid, U/A, urine C&amp;S</th>
<th>KUB x-ray</th>
<th>CT scan</th>
<th>Abdominal ultrasound</th>
<th>Cystoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT shows stone</td>
<td>CT shows no stone – Consider alternate causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KUB x-ray</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Urgent Intervention required if:
1. Solitary kidney
2. Bilateral stones
3. Intractable pain or vomiting
4. Acute renal failure

Non-urgent pathway

Likelihood of stone passage

Low

High

Uric acid stone

Non-uric acid stone

Intervention

Observation

**Dissolution therapy**

**ESWL** (Ureteroscopy, PCNL)

**Stent/Nephrostomy**

**Treatment – Acute**

- medical
  - analgesic ± antiemetic
  - NSAIDs help lower intra-ureteral pressure
  - medical expulsion therapy (MET)
    - α-blockers: increase rate of spontaneous passage in distal ureteral stones
    - calcium channel blockers
    - ± Abx for bacteriuria
    - IV fluids if vomiting (note: IV fluids do NOT promote stone passage)
  - interventional
    - required if obstruction endangers patient, e.g. sepsis, renal failure
    - first line: ureteric stent (via cystoscopy)
    - second line: image-guided percutaneous nephrostomy
  - admit if necessary
  - see sidebar: *Indications for Admission to Hospital*

**Treatment – Elective**

- medical
  - likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
  - stones <3 mm especially likely to pass spontaneously
  - PO fluids to increase urine volume to >2 L/d (3-4 L if cystine) and MET
  - specific to stone type (see Table 13)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)

---

**Indications for Admission to Hospital**

- Intractable pain
- Intractable vomiting
- Fever (suggests infection)
- Compromised renal function (including single kidney, bilateral obstructing stone)
- Pregnancy

**Stones and Infection**

If septic, urgent decompression via ureteric stent or percutaneous nephrostomy is indicated. Definitive treatment of the stone should be delayed until the sepsis has cleared

---

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    - calcium channel blockers
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    - required if obstruction endangers patient, e.g. sepsis, renal failure
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  - specific to stone type (see Table 13)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)
- interventional
  - kidney
    - may stent prior to ESWL if stone is 1.5-2.5 cm
    - ESWL if stone <2 cm
    - PCNL if stone >2 cm
  - ureteral stones >10 mm
  - ESWL and URS are both first line treatment modalities for all locations
    - URS has significantly greater stone-free rates for stones at all locations in ureter, but also has higher complication rates (ureter perforation, stricture formation, etc.)
  - PCNL is second line treatment
  - laparoscopic or open stone removal (very rare)
- bladder
  - transurethral stone removal or cystolitholapaxy
  - remove outflow obstruction (TURP or stricture dilatation)

Prevention
- dietary modification
  - increase fluid (>2 L/d), K+ intake
  - reduce animal protein, oxalate, Na+, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
- medications
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria

**Table 13. Stone Classification**

<table>
<thead>
<tr>
<th>Type of Stone</th>
<th>Calcium (75-85%)</th>
<th>Uric Acid (5-10%)</th>
<th>Struvite (5-10%)</th>
<th>Cystine (1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Hypercalciuria</td>
<td>Uric acid precipitates in low volume, acidic urine with a high uric acid concentration</td>
<td>Infection with urea-splitting organisms (Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)</td>
<td>Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in “COLA” in urine (cystine, ornithine, lysine, arginine)</td>
</tr>
<tr>
<td></td>
<td>Hyperuricosuria (25% of patients with Ca&lt;sup&gt;2+&lt;/sup&gt; stones)</td>
<td>Hyperuricosuria alone</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperoxaluria (&lt;5% of patients)</td>
<td>Low urinary pH, low urine volume (e.g. GI water loss)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypocitraturia (12% of patients)</td>
<td>Hyperuricosuria with hypocitruria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other causes</td>
<td>Diet (purine rich red meats)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypomagnesemia – associated with hyperoxaluria and hypocitraturia</td>
<td>Hyperuricosuria with hypocitruria</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High dietary Na&lt;sup&gt;+&lt;/sup&gt;</td>
<td>Gout</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreased urinary proteins</td>
<td>High rate of cell turnover or cell death (leukemia, cytotoxic drugs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High urinary pH, low urine volume (e.g. GI water loss)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperparathyroidism, obesity, gout, DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key Features</td>
<td>Radiopaque on KUB</td>
<td>Radiolucent on KUB</td>
<td></td>
<td>Aggressive stone disease seen in children and young adults</td>
</tr>
<tr>
<td></td>
<td>Reducing dietary Ca&lt;sup&gt;2+&lt;/sup&gt; is NOT an effective method of prevention/ treatment</td>
<td>Acidic urine, pH &lt; 5.5 (NOT necessarily elevated urinary uric acid)</td>
<td></td>
<td>Recurrent stone formation, family Hx</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Perpetuates UTI because stone itself harbours organism Stone and all foreign bodies must be cleared to avoid recurrence Associated with staghorn calculi Positive urine dip and cultures Note: E. coli infection does not cause struvite stones M:F = 3:1, UTI more common in female</td>
<td></td>
<td>Often staghorn calculi Faintly radiopaque on KUB Positive urine sodium nitroprusside test, urine chromatography for cystine</td>
</tr>
<tr>
<td>Treatment</td>
<td>Fluids to increase urine volume to &gt;2 L/d</td>
<td>Increased fluid intake</td>
<td>Complete stone clearance</td>
<td>Increased fluid intake (3-4 L of urine/d)</td>
</tr>
<tr>
<td>Medical if stone &lt;5 mm and no complications</td>
<td>For calcium stones: cellulose phosphate, orthophosphate for absorptive causes Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol Calcium struvite: ABx (stone must be removed to treat infection)</td>
<td>Alkalization of urine to pH 6.5 to 7 (bicarbonate, potassium citrate) ± allopurinol</td>
<td>ABx for 6 wk Regular follow-up urine cultures</td>
<td>Alkalize urine (bicarbonate, potassium citrate), Penicillamine/ α-MPG or Captopril (form complex with cystine)</td>
</tr>
<tr>
<td>Procedural/Surgical treatment if stone &gt;5 mm or presence of complications (see U17 for treatment)</td>
<td>Calcium oxalate: thiazides, ± potassium citrate, ± allopurinol Calcium struvite: ABx (stone must be removed to treat infection)</td>
<td></td>
<td></td>
<td>ESWL not effective</td>
</tr>
</tbody>
</table>
Urological Neoplasms

Approach to Renal Mass

**Figure 9. Workup of a renal mass**
*Imaging modality may be different in cases of contrast allergy or elevated creatinine

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Features</th>
<th>Risk of Malignancy</th>
<th>Management Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Simple cyst</td>
<td>Round, no septations, no calcifications, no solid component</td>
<td>Near zero</td>
<td>Follow-up usually not required</td>
</tr>
<tr>
<td>II</td>
<td>Simple cyst</td>
<td>A few thin septa, no true enhancement, well-margined, uniform high attenuation, &lt;3 cm</td>
<td>Minimal</td>
<td>Follow-up usually not required</td>
</tr>
<tr>
<td>IIII</td>
<td>Minimally complex cyst with extra features that require follow-up</td>
<td>Still well-margined and non-enhancing, but now multiple thin septa or some thickening/calcification of septa/wall, &gt;3 cm</td>
<td>5-20%</td>
<td>Requires follow-up with imaging q6-12 mo If the lesion evolves, may require surgical resection</td>
</tr>
<tr>
<td>III</td>
<td>Complex cyst</td>
<td>Thicker or more irregular walls with measurable enhancement</td>
<td>&gt;50%</td>
<td>Requires surgical resection</td>
</tr>
<tr>
<td>IV</td>
<td>Clearly malignant</td>
<td>Class III + enhancing soft-tissue components</td>
<td>&gt;90%</td>
<td>Requires surgical resection</td>
</tr>
</tbody>
</table>

Benign Renal Neoplasms

**CYSTIC KIDNEY DISEASE**
- **Simple cysts**: usually solitary or unilateral
  - usually incidental finding on abdominal imaging
  - **Bosniak Classification** is used to stratify for risk of malignancy based on cyst features from contrast CT
- **Polycystic kidney disease**
  - Autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - Autosomal dominant: progressive bilateral disease leading to HTN and renal failure, adult-onset
- **Medullary sponge kidney**: cystic dilatation of the collecting ducts
  - Usually benign course, but patients are predisposed to stone disease
- **von Hippel-Lindau syndrome**: multiple bilateral cysts or clear cell carcinomas (50% incidence of RCC)
  - Renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

**Tuberous Sclerosis**
Syndrome characterized by mental retardation, epilepsy, and adenoma sebaceum. 45-80% of patients also present with angiomylipomas which are often multiple and bilateral

**Percutaneous needle biopsies of cystic renal masses may lead to peritoneal seeding**

Table 14. Bosniak Classification of Renal Cysts
Table 15. Benign Renal Masses

<table>
<thead>
<tr>
<th>Angiomyolipoma (Renal Hamartoma)</th>
<th>Renal Oncocytoma</th>
<th>Renal Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1% of adult renal tumors</td>
<td>3-7% of renal tumors</td>
<td>Most common benign renal neoplasm</td>
</tr>
<tr>
<td>F&gt;M</td>
<td>M&gt;F</td>
<td>M:F = 3:1</td>
</tr>
<tr>
<td>20% associated with tuberous sclerosis (especially if multiple, recurrent)</td>
<td>Oncocytomas also found in adrenal, thyroid and parathyroid glands</td>
<td>Incidence increases with age</td>
</tr>
<tr>
<td></td>
<td>Spherical, capulated with possible central scar</td>
<td>Found in 7-23% of all autopsies</td>
</tr>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma)</td>
<td>Spherically organized aggregates of eosinophilic cells originating from intercalated cells of collecting duct</td>
<td>Small cortical lesions &lt;1 cm</td>
</tr>
<tr>
<td>May extend into regional lymphatics and other organs and become symptomatic</td>
<td></td>
<td>Majority are solitary but can be multifocal</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidental finding on CT</td>
<td>Incidental finding on CT</td>
<td>Incidental finding on CT</td>
</tr>
<tr>
<td>Negative attenuation (&lt;20 HU) on CT is pathognomonic</td>
<td>Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise</td>
<td>Rarely symptomatic</td>
</tr>
<tr>
<td>Rare presentation of hematuria, flank pain, and palpable mass (same as RCC)</td>
<td>Biopsy may be performed to rule out malignancy</td>
<td>Controversy as to whether this represents benign or pre-malignant neoplasm</td>
</tr>
<tr>
<td>Management</td>
<td></td>
<td></td>
</tr>
<tr>
<td>May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy)</td>
<td>Partial/radical nephrectomy for large masses</td>
<td>If mass &gt;3 cm, likely not a benign adenoma; will require partial/radical nephrectomy due to increased likelihood of malignancy</td>
</tr>
<tr>
<td>Potential role for mTOR inhibitors in unresectable/metastatic disease</td>
<td>HIFU or RFA for smaller masses</td>
<td></td>
</tr>
<tr>
<td>Follow with serial U/S</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Malignant Renal Neoplasms

RENAL CELL CARCINOMA

Etiology
- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

Epidemiology
- 8th most common malignancy (accounts for 3% of all newly diagnosed cancers)
- 85% of primary malignant tumors in kidney
- M:F = 3:2
- peak incidence at 50-60 yr of age

Pathology
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobic (5-10%), collecting duct
- sarcomatoid elements in any subtype is a poor prognostic factor

Risk Factors
- top 3 risk factors: smoking, HTN, obesity
- miscellaneous: horseshoe kidney, acquired renal cystic disease
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

Clinical Features
- usually asymptomatic: frequently diagnosed incidentally by U/S or CT
- poor prognostic indicators: weight loss, weakness, anemia, bone pain
- classic “too late triad” found in 10-15%
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- was called the “internist’s tumor” because of paraneoplastic symptomatology – now called the “radiologist’s tumor” because of incidental diagnosis via imaging
- metastases: seen in 1/3rd of new cases; additional 20-40% will go on to develop metastases
  - bone, brain, lung and liver most common site
  - may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumor, and pulmonary emboli

Investigations
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A (60-75% have hematuria)
- renal U/S: solid vs. cystic lesion
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

RCC Systemic Effects: paraneoplastic syndromes (10-40% of patients)
- Hematopoietic disturbances: anemia, polycythemia, raised ESR
- Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)
- Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumor
- Hemodynamic alterations: systolic HTN (due to AV shunting), peripheral edema (due to caval obstruction)
• contrast-enhanced CT: higher sensitivity than US for detection of renal masses and for staging purposes
• MRI: useful for evaluation of vascular extension
• renal biopsy: to confirm diagnosis if considering observation or other non-surgical therapy

Staging
• involves CT, CXR, liver enzymes and LFTs, bone/head imaging (if symptoms dictate)

Table 16. 2010 TNM Classification of Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>tumor &lt;7 cm, confined to renal parenchyma</td>
<td>N0: no regional nodes</td>
</tr>
<tr>
<td>T1a</td>
<td>&lt;4 cm</td>
<td>N1: metastasis to a single node, &lt;2 cm</td>
</tr>
<tr>
<td>T1b</td>
<td>4-7 cm</td>
<td>N2: metastasis to a single node between 2 and 5 cm or multiple nodes &lt;2 cm</td>
</tr>
<tr>
<td>T2</td>
<td>tumor &gt;7 cm, confined to renal parenchyma</td>
<td>N3: node &gt;5 cm</td>
</tr>
<tr>
<td>T2a</td>
<td>tumor &gt;7 cm but ≤10 cm in greatest dimension, limited to the kidney</td>
<td></td>
</tr>
<tr>
<td>T2b</td>
<td>tumor &gt;10 cm, limited to the kidney</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>tumor extends into major veins or peripheric tissues, but NOT into ipsilateral adrenal or beyond Gerota’s fascia</td>
<td></td>
</tr>
<tr>
<td>T3a</td>
<td>into renal vein or sinus fat</td>
<td></td>
</tr>
<tr>
<td>T3b</td>
<td>into infradiaphragmatic IVC</td>
<td></td>
</tr>
<tr>
<td>T3c</td>
<td>into supradiaphragmatic IVC</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>tumor extends beyond Gerota’s fascia including extension into ipsilateral adrenal</td>
<td></td>
</tr>
</tbody>
</table>

Treatment
• surgical
  ▪ radical nephrectomy: en bloc removal of kidney, tumor, ipsilateral adrenal gland (in upper pole tumors) and intact Gerota’s capsule and paraaortic lymphadenectomy
  ▪ partial nephrectomy (parenchyma-sparing): small tumor (roughly <4 cm) or solitary kidney/bilateral tumors
  ▪ surgical removal of solitary metastasis may be considered
  ▪ ablative techniques (cryoablation, RFA)
  ▪ palliative radiation to painful bony lesions
  ▪ therapy for advanced stage
  ▪ tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)
  ▪ anti-angiogenesis/anti-VEGF (e.g. bevacizumab)
  ▪ mTOR inhibitors (e.g. temsirolimus, everolimus)
  ▪ high-dose IL-2 (high toxicity but able to induce long-term cure in 5-7% of patients)
  ▪ IFN α: monotherapy has been largely replaced by molecularly targeted agents listed above

Prognosis
• stage at diagnosis most important prognostic factor
  ▪ T1: 90-100% 5 yr survival
  ▪ T2-T3: 60% 5 yr survival
  ▪ metastatic disease: <5% 10 yr survival

Carcinoma of the Renal Pelvis and Ureter

Etiology
• risk factors include
  ▪ smoking
  ▪ chemicals/dietary exposures (industrial dyes and solvents; aristolochic acid)
  ▪ analgesic abuse (acetaminophen, ASA, and phenacetin)
  ▪ Balkan nephropathy

Epidemiology
• rare: accounts for 5% of all urothelial cancers
• frequently multifocal, 2-5% are bilateral
• M:F = 3:1
• relative incidence: bladder:renal:ureter = 100:10:1

Pathology
• 85% are papillary UCC; others include SCC and adenocarcinoma
• UCC of ureter and renal pelvis are histologically similar to bladder UCC

Clinical Features
• gross/microscopic hematuria
• flank pain
• storage or voiding symptoms (dysuria only if lower urinary tract involved)
• flank mass ± hydronephrosis (10-20%)
Investigations
- IVP/CT urogram
- cystoscopy and retrograde pyelogram

Treatment
- radical nephroureterectomy with cuff of bladder
- distal ureterectomy for distal ureteral tumors
- emerging role for endoscopic laser ablation in patients with low grade disease, poor baseline renal health

Bladder Carcinoma

Etiology
- unknown, but environmental risk factors include
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior Hx of radiation treatment to the pelvis
  - Schistosoma hematothium infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)
  - aristolochic acid: associated with Balkan Nephropathy (renal failure, upper tract urothelial cancer) and Chinese Herbal Nephropathy

Epidemiology
- 2nd most common urological malignancy
- M:F = 3:1, more common among whites than blacks
- mean age at diagnosis is 65 yr

Pathology
- classification
  - UCC >90%
  - SCC 5-7%
  - adenocarcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis
  - non-muscle invasive (75%) → >80% overall survival
  - the majority of these patients will have recurrence
  - invasive (25%) → 50-60% 5 yr survival
  - 85% have no prior hx of superficial UCC (i.e. de novo)
  - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma in situ → flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive UCC

Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) → location determined by size/extent of tumor (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms → consider carcinoma in situ
- palpable mass on bimanual exam → likely muscle invasion
- obstruction of ureters → hydronephrosis and uremia (nausea, vomiting, and diarrhea)

Investigations
- U/A, urine C&S, urine cytology
- U/S
  - CT scan with contrast → look for filling defect
- cystoscopy with biopsy (gold standard)
  - biopsy to establish diagnosis and to determine depth of penetration
- specific bladder tumor markers (e.g. NMP-22, BTA, Immunocyt, FDP)

Grading
- low grade: <=10% invasive, 60% recur
- high grade: 50-80% are invasive or should progress to invasive over time

Staging
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes (Ca^{2+}, Mg^{2+}, PO_{4}^{3-}) (metastatic workup)
Table 17. 2010 TNM Classification of Bladder Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX:</td>
<td>N:</td>
<td>M: No</td>
</tr>
<tr>
<td>TX:</td>
<td>Lymph</td>
<td>distant</td>
</tr>
<tr>
<td>T0:</td>
<td>nodes cannot be assessed</td>
<td>metastasis</td>
</tr>
<tr>
<td>T1a:</td>
<td>No</td>
<td>T0: No</td>
</tr>
<tr>
<td>T1b:</td>
<td>evidence of primary tumor</td>
<td>lymph node metastasis</td>
</tr>
<tr>
<td>T2a:</td>
<td>Carcinoma in situ</td>
<td>T1: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)</td>
</tr>
<tr>
<td>T2b:</td>
<td>Carcinoma</td>
<td>T1: Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)</td>
</tr>
<tr>
<td>T3:</td>
<td>Carcinoma</td>
<td>T2: Lymph node metastasis to the common iliac lymph nodes</td>
</tr>
<tr>
<td>T4a:</td>
<td>Carcinoma</td>
<td>T3: 5% 5 yr survival</td>
</tr>
<tr>
<td>T4b:</td>
<td>Carcinoma</td>
<td>T4: &lt;5% 5 yr survival</td>
</tr>
</tbody>
</table>

Figure 11. Urothelial carcinoma of bladder

Treatment
- superficial (non-muscle invasive) disease: Tis, Ta, T1
  - low-grade disease
    - single dose mitomycin c within 24 h of resection reduces recurrence rates
  - high-grade
    - TURBT + intravesical chemo/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
    - maintenance with intravesical chemotherapy with BCG for 3 cycles every 3 mo, may be continued for 2-3 yr
- invasive disease: T2a, T2b, T3
  - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileal conduit, Indiana pouch, ileal neobladder) or TURBT + chemo-radiation (bladder sparing) for small tumors with non-obstructed ureters
  - neo-adjuvant chemotherapy prior to cystectomy may also be done
  - use of adjuvant chemotherapy after definitive local treatment is controversial
- advanced/metastatic disease: T4a, T4b, N+, M+
  - initial combination of systemic chemotherapy ± irradiation ± surgery

Prognosis
- depends on stage, grade, size, number of lesions, recurrence and presence of CIS
  - T1: 90% 5 yr survival
  - T2: 55% 5 yr survival
  - T3: 20% 5 yr survival
  - T4/N+/M+: <5% 5 yr survival

Prostate Cancer

Etiology
- not known
- risk factors
  - increased incidence in persons of African descent
  - high dietary fat = 2x risk
family Hx
- 1st degree relative = 2x risk
- 1st and 2nd degree relatives = 9x risk

**Epidemiology**
- most prevalent cancer in males
- 3rd leading cause of male cancer deaths (following lung and colon)
- up to 50% risk of CaP at age 50
- lifetime risk of death from CaP is 3%
- 75% diagnosed between 60-85 yr; mean age at diagnosis is 72

**Pathology**
- adenocarcinoma
  - >95%, often multifocal
- urothelial carcinoma of the prostate (4.5%)
  - associated with UCC of bladder; does NOT follow TNM staging below; not hormone-responsive
- endometrial (rare)
  - carcinoma of the utricle

**Anatomy** (see Figure 7, U7)
- 60-70% of nodules arise in the peripheral zone
- 10-20% arise in the transition zone
- 5-10% arise in the central zone

**Clinical Features**
- usually asymptomatic
- most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  - DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  - PSA: see *Prostate Cancer Screening*, U25
- locally advanced disease
  - storage and voiding symptoms, ED (all uncommon without spread)
  - metastatic disease
    - bony mets to axial skeleton common
    - visceral mets are less common (liver, lung, and adrenal gland most common sites)
    - leg pain and edema with nodal mets obstructing lymphatic and venous drainage

**Methods of Spread**
- local invasion
- lymphatic spread to regional nodes
  - obturator > iliac > presacral/para-aortic
- hematogenous dissemination occurs early

**Investigations**
- DRE
- PSA elevated in the majority of patients with CaP
- TRUS-guided needle biopsy
- bone scan may be omitted in untreated CaP with PSA <10 ng/mL
- CT scanning to assess metastases
- MRI: being investigated for possible role in detection, staging, MRI-guided biopsying and active surveillance

**Table 18. 2010 TNM Classification of Prostate Carcinoma**

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1:</td>
<td>clinically undetectable tumor, normal DRE and TRUS</td>
<td>N0: no regional lymph node metastasis</td>
</tr>
<tr>
<td>T1a:</td>
<td>tumor incidental histologic finding in &lt;5% of tissue resected</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T1b:</td>
<td>tumor incidental histologic finding in &gt;5% of tissue resected</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T1c:</td>
<td>tumor identified by needle biopsy (due to elevated PSA level)</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T2:</td>
<td>palpable, confined to prostate</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T2a:</td>
<td>tumor involving ≤ one half of one lobe</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T2b:</td>
<td>tumor involving &gt; one half of one lobe, but not both lobes</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T2c:</td>
<td>tumor involving both lobes</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T3:</td>
<td>tumor extends through prostate capsule</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T3a:</td>
<td>extracapsular extension (unilateral or bilateral)</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T3b:</td>
<td>tumor invading seminal vesicle(s)</td>
<td>N1: spread to regional lymph nodes</td>
</tr>
<tr>
<td>T4:</td>
<td>tumor invades adjacent structures (besides seminal vesicles)</td>
<td>NX: regional lymph nodes were not assessed</td>
</tr>
</tbody>
</table>
Prostate Specific Antigen

- PSA: velocity, density, and free:total PSA: all intended to increase sensitivity and specificity.
- Measured serum PSA is a combination of free (15%) and bound PSA (85%).
- Value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathological.
- Leaks into circulation in setting of disrupted glandular architecture.
- Glycoprotein produced by epithelial cells of prostate gland.

Digital Rectal Exam

- Suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture.
- Should be included as part of initial screening.

Prognosis

- T1-T2: comparable to normal life expectancy.
- T3-T4: 40-70% 10 yr survival.
- N+ and/or M+: 40% 5 yr survival.
- Prognostic factors: tumor stage, tumor grade, PSA value, PSA doubling time.

Prostate Cancer Screening

- Digital Rectal Exam: should be included as part of initial screening.
- Prostate Specific Antigen: glycoprotein produced by epithelial cells of prostate gland.

Screening Recommendations

- Conflicting evidence regarding mortality reduction with PSA-based screening and debate regarding overdiagnosis/overtreatment.

Table 19. Prostate Cancer Mortality Risk

<table>
<thead>
<tr>
<th>Stage</th>
<th>Low Risk</th>
<th>Intermediate Risk (if any of following)</th>
<th>High Risk (if any of following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &lt;10</td>
<td>10-20</td>
<td>&gt;20</td>
<td></td>
</tr>
<tr>
<td>Gleason &lt;7</td>
<td>7</td>
<td>8-10</td>
<td></td>
</tr>
<tr>
<td>pT1-T2a</td>
<td>pT2b-T2c</td>
<td>pT3/T4</td>
<td></td>
</tr>
</tbody>
</table>

Table 20. Treatment Options for Localized Prostate Cancer

<table>
<thead>
<tr>
<th>Modality</th>
<th>Population Considered</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful Waiting</td>
<td>Short life expectancy (&lt;5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses</td>
<td>Disease progression</td>
</tr>
<tr>
<td>Active Surveillance (Serial PSA, DRE, and Biopsies)</td>
<td>Low grade disease, good follow-up; is still considering more curative treatment if disease progresses</td>
<td>Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Low volume, low PSA (&lt;10), low grade</td>
<td>ED (50%), long-term effectiveness not well-established</td>
</tr>
<tr>
<td>EBRT</td>
<td>Locally advanced disease, older patients</td>
<td>Radiation proctitis (5%), ED (50%), risk of rectal cancer</td>
</tr>
<tr>
<td>Watchful Waiting</td>
<td>Young patients (&lt;75 yr), high-risk disease</td>
<td>Incontinence (10%), ED (30-50%)</td>
</tr>
</tbody>
</table>

*Other options include cryosurgery, HIFU, hormonal ablation.

Radical Prostatectomy vs. Watchful Waiting

= Early Prostate Cancer (Scandinavian Prostate Cancer Group Study)
Study: Randomized clinical trial comparing watchful waiting with radical prostatectomy for localized prostate cancer.
Methods: 699 men from 14 centers in Finland, Sweden, and Iceland with newly diagnosed, localized prostate cancer were included in this study.
Main Outcomes: Mortality, distant metastases, local progression.
Results: For men with low-risk prostate cancer (PSA<10, Gleason score<7), at 15 yr after treatment initiation, the relative risk of death due to prostate cancer in the radical prostatectomy group vs. watchful waiting was 0.62 (p=0.01). The cumulative incidence of death from prostate cancer after radical prostatectomy was high as compared with other studies.
Conclusions: Radical prostatectomy was associated with reduced rate of death due to prostate cancer.

Radical Prostatectomy vs. Observation for Localized Prostate Cancer. (Prostate Cancer Intervention vs. Observation Trial (PIVOT) Study Group)
Study: Randomized clinical trial comparing observation vs. radical prostatectomy for localized prostate cancer.
Methods: 731 men at 52 United States centers with localized prostate cancer participated.
Main Outcomes: Mortality, bone metastases, surgical morbidity.
Results: Radical prostatectomy did not reduce all-cause or prostate cancer mortality relative to observation (relative risk 0.60, p=0.09), through at least 12 yr of follow-up.
Conclusions: Observation is recommended for localized prostate cancer, especially in men with low PSA and low-risk disease.

Causes of Increased PSA

- BPH, prostatectasis, perianal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy.

PSA is specific to the PROSTATE, but NOT to prostate cancer.
 Ontario Ministry of Health and Long-Term Care and United States Preventative Services Task Force both recommend against PSA testing as a population-wide screening tool

however, serum PSA screening recommended in any man with >10 yr life-expectancy and any of the following:
- suspicious finding on DRE
- moderate-severe LUTS
- high risk individuals
- investigating secondary carcinoma of unknown origin to r/o CaP as primary

American Urological Association Guidelines (2013) re: Prostate Cancer Screening

- men under age 40 yr should not have PSA screening (Grade C)
- men aged 40-54 yr should not be screened, unless they have high risk factors (e.g. positive family history or African American race), screening decisions should be individualized (Grade C)
- men aged 55-69 yr should proceed with screening only after shared decision-making on the basis of their values and preferences (Grade B)
- routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening (Grade C)
- men aged 70+ years or any man with less than a 10-15 yr life expectancy should not have PSA screening

Testicular Tumors

Etiology/Risk Factors
- cryptorchidism, atrophy, sex hormones, HIV infection, infertility, family hx, past hx of testicular cancer

Epidemiology
- rare, but most common solid malignancy in young males 15-34 yr
- any solid testicular mass or acute hydrocele in young patient – must r/o malignancy
- slightly more common in right testis (corresponds with slightly higher incidence of right-sided cryptorchidism)
- 2-3% bilateral (simultaneously or successively)

Pathology
- primary
  - 1% of all malignancies in males
  - cryptorchidism has increased risk (10-40x) of malignancy
  - 95% are germ cell tumors (all are malignant)
    - seminoma (35%) → classic, anaplastic, spermatocytic
    - NSGCT → embryonal cell carcinoma (20%), teratoma (5%), choriocarcinoma (<1%), yolk sac (<1%), mixed cell type (40%)
  - 5% are non-germ cell tumors (usually benign) → Leydig (testosterone, precocious puberty), Sertoli (gynecomastia, decreased libido)
- secondary
  - male >50 yr
  - usually lymphoma or metastases (e.g. lung, prostate, GI)

Clinical Features
- painless testicular enlargement (painful if intratesticular hemorrhage or infarction)
- dull, heavy ache in lower abdomen, anal area or scrotum
- associated hydrocele (10%)
- coincidental trauma (10%)
- infertility (rarely presenting complaint)
- gynecomastia due to secretory tumor effects
- supraclavicular and inguinal lymphadenopathy
- abdominal mass (retroperitoneal lymph node mets)

Methods of Spread
- local spread follows lymphatics
  - right → medial, paracaval, anterior and lateral nodes
  - left → left lateral and anterior paraaortic nodes
  - "cross-over" metastases from right to left are fairly common, but no reports from left to right
- hematogenous most commonly to lung, liver, bones, and kidney

Investigations
- diagnosis is established by pathological evaluation of specimen obtained by radical inguinal orchidectomy
- tumor markers (β-hCG, LDH, AFP)
  - β-hCG and AFP are positive in 85% of non-seminomatous tumors
  - elevated marker levels return to normal post-operatively if no metastasis
  - β-hCG positive in 7% of pure seminomas, AFP never elevated with seminoma
- testicular U/S (hypoechoc area within tunica albuginea = high suspicion of testicular cancer)
- evidence of testicular microlithiasis is not a risk factor for testicular cancer
- needle aspiration contraindicated
Staging
- Clinical: CXR (lung mets), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)
  - Stage I: disease limited to testis, epididymis, or spermatic cord
  - Stage II: disease limited to the retroperitoneal nodes
  - Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

Table 21. 2010 TNM Classification of Testicular Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis: intratubular germ cell neoplasia</td>
<td>N status: same as RCC</td>
<td>M0: no distant mets</td>
</tr>
<tr>
<td>T1: Limited to testis and epididymis without vascular/lymphatic invasion</td>
<td></td>
<td>M1: distant mets</td>
</tr>
<tr>
<td>T2: Limited to testis and epididymis with vascular/lymphatic invasion</td>
<td></td>
<td>M1a: nonregional lymph node(s) or pulmonary mets</td>
</tr>
<tr>
<td>T3: Invasion of the spermatic cord ± vascular/lymphatics</td>
<td></td>
<td>M1b: distant mets other than to regional lymph nodes and lung</td>
</tr>
<tr>
<td>T4: Invasion of the scrotum ± vascular/lymphatics</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management
- orchiectomy through inguinal ligament for all stages
- consider sperm banking, testicular prosthesis
- adjuvant therapies

Prognosis
- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

Penile Tumors

Epidemiology
- rare (<1% of cancer in males in U.S.)
- most common in 6th decade

Benign
- cyst, hemangioma, nevus, papilloma

Pre-Malignant
- balanitis xerotica obliterans, leukoplakia, Buschke-Lowenstein tumor (large condyloma)

Pre-Invasive Cancer
- carcinoma in situ (CIS)
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvety, red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil

Malignant
- risk factors
  - chronic inflammatory disease
  - STD
  - phimosis
  - uncircumcised penis
  - 2% of all urogenital cancers
  - SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
- definitive diagnosis requires full thickness biopsy of lesion
- lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous
Treatment
• wide surgical excision with tumor-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
• consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available

### Table 22. Differentiating between Scrotal Masses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pain</th>
<th>Palpation</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsion</td>
<td>+</td>
<td>Diffuse tenderness</td>
<td>Absent cremaster reflex, negative Phren’s sign</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>(U15) +</td>
<td>Epidymal tenderness</td>
<td>Present cremaster reflex, positive Phren’s sign</td>
</tr>
<tr>
<td>Orchitis</td>
<td>(U15) +</td>
<td>Diffuse tenderness</td>
<td>Present cremaster reflex, positive Phren’s sign</td>
</tr>
<tr>
<td>Hematocoele</td>
<td>+</td>
<td>Diffuse tenderness</td>
<td>No transillumination</td>
</tr>
<tr>
<td>Hydroscele</td>
<td>–</td>
<td>Testis not separable from hydroscele, cord palpable</td>
<td>Transillumination, Hx of trauma</td>
</tr>
<tr>
<td>Spermatocele</td>
<td>–</td>
<td>Testis separable from spermatocele, cord palpable</td>
<td>Transillumination</td>
</tr>
<tr>
<td>Varicocele</td>
<td>–</td>
<td>Bag of worms</td>
<td>No transillumination, increases in size with Valsalva, decrease in size if supine</td>
</tr>
<tr>
<td>Indirect Inguinal</td>
<td>– (± if strangulated)</td>
<td>Testis separable from hernia, cord palpable, cough impulse may transmit, may be reducible</td>
<td>No transillumination</td>
</tr>
<tr>
<td>Tumor</td>
<td>– (± if hemorrhagic)</td>
<td>Hard lump/nodule</td>
<td></td>
</tr>
<tr>
<td>Generalized/ Dependant Edema</td>
<td>–</td>
<td>Diffuse swelling</td>
<td>Often post-operative or immobilized, check for liver dysfunction</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 23. Benign Scrotal Masses

<table>
<thead>
<tr>
<th>Type</th>
<th>Varicocele</th>
<th>Spermatocele</th>
<th>Hydrocele</th>
<th>Testicular Torsion</th>
<th>Inguinal Hernia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Dilatation and tortuosity of pampiniform plexus</td>
<td>A benign, sperm filled epididymal retention cyst</td>
<td>Collection of serous fluid that results from a defect or irritation in the tunica vaginalis</td>
<td>Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction</td>
<td>Protrusion of abdominal contents through the inguinal canal into the scrotum</td>
</tr>
<tr>
<td>Etiology</td>
<td>15% of men Due to incompetent valves in the testicular veins 90% left sided</td>
<td>Multiple theories, including: Distal obstruction Aneurysmal dilations of the epididymis Agglutinated germ cells</td>
<td>Usually idiopathic Found in 5-10% testicular tumors Associated with trauma/ infection Communicating: patent processus vaginalis, changes size during day (peds) Non-communicating: non-patient processus vaginalis (adult)</td>
<td>Trauma Cryptorchidism “Bell clapper deformity” Many occur in sleep (50%) Necrosis of glands in 5-6 h</td>
<td>Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness</td>
</tr>
<tr>
<td>Hx/P/E</td>
<td>“Bag of worms” Often painless Pulsates with Valsalva</td>
<td>Non-tender, cystic mass Transilluminates</td>
<td>Non-tender, intrascrotal mass Cystic Transilluminates</td>
<td>Acute onset severe scrotal pain, swelling GI upsets cases Retracted and transverse testicle (horizontal lie) Negative Phren’s sign Absent cremasteric reflex</td>
<td>A small bulge in the groin that may increase in size with Valsalva and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising</td>
</tr>
<tr>
<td>Investigations</td>
<td>P/E Valsalva P/E U/S to r/o tumor</td>
<td>U/S to r/o tumor</td>
<td>U/S with color flow Doppler probe over testicular artery Decrease uptake on 99mTc-pertechnetate scintillation scan (doughnut sign)</td>
<td>Hx and P/E Invagination of the scrotum Valsalva</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (balloon, sclerosing agents) Repair may improve sperm count/motility 50-75%</td>
<td>Conservative Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum Excise if symptomatic</td>
<td>Conservative Needle drainage Surgical</td>
<td>Emergency surgical exploration and bilateral orchiectomy Orchiectomy if poor prognosis</td>
<td>Surgical repair</td>
</tr>
</tbody>
</table>
TORSION OF TESTICULAR APPENDIX
- twisting of testicular/epididymal vestigial appendix

Signs and Symptoms
- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
  - “blue dot sign”
  - blue infarcted appendage seen through scrotal skin (can usually be palpated as small, tender lump)

Treatment
- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

HEMATOCELE
- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

Penile Complaints

<table>
<thead>
<tr>
<th>Table 24. Penile Complaints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
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<tr>
<td>Definition</td>
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<tr>
<td>Etiology</td>
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<td>Hx/P/E</td>
</tr>
<tr>
<td>Investigations</td>
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<td>Treatment</td>
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Erectile Dysfunction

Definition
• consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

Physiology
• erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
• nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic (dorsal penile/pudendal nerves [S2-4])
• erection (“POINT”)
  - parasympathetics → release of nitric oxide (NO) → increased cGMP levels within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
• emission (“SHOOT”)
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
• ejaculation (“SHOOT”)
  - bladder neck closure (sympathetic)
  - spasmotic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
• detumescence
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

Classification

Table 25. Classification of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Psychogenic</th>
<th>Organic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>10%</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden</td>
</tr>
<tr>
<td>Frequency</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Variation</td>
<td>With partner and circumstance</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
</tr>
<tr>
<td>Organic Risk Factors (HTN, DM, Dyslipidemia)</td>
<td>No organic risk factors</td>
</tr>
<tr>
<td>Nocturnal/AM Erection</td>
<td>Present</td>
</tr>
</tbody>
</table>

Etiology (“IMPOTENCE”)
• Iatrogenic: pelvic surgery, pelvic radiation
• Mechanical: Peyronie’s, post-priapism
• Psychologic: depression, stress, anxiety, PTSD, widower syndrome
• Occlusive vascular: arterial HTN, DM, smoking, hyperlipidemia, PVD, venous (impaired veno-occlusion)
• Trauma: penile/pelvic, bicycling
• Extra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
• Neurogenic: CNS (e.g. Parkinson’s, MS, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
• Chemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, anticholinergics, antihistamines, anti-androgens (including 5-α reductase inhibitors), statins, GnRH agonists, illicit drugs
• Endocrine: DM, hypogonadism, hyperprolactinemia, hypo/hyperthyroid

Diagnosis
• complete Hx (include sexual, medical, and psychosocial aspects)
• self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
• focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
• lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
• specialized testing including nocturnal penile tumescence monitoring usually unnecessary
• evaluation of penile vasculature only relevant with past history of trauma (i.e. pelvic fracture)
Treatment
- can often be managed by family doctor, see sidebar for when to refer
- must fully inform patient/partner of options, benefits and complications
- non-invasive
  - lifestyle changes (alcohol, smoking), psychological (sexual counseling and education)
  - change precipitating medications
  - treat underlying causes (diabetes, CVD, HTN, endocrinopathies)
- minimally invasive
  - oral medication (see Common Medications, U42)
    - sildenafil, tadalafil, vardenafil, avanafil: inhibits PDE-5 to increase intracavernosal cyclic GMP levels
      - all four have similar effectiveness, but tadalafil has certain advantages: earlier onset, longer half-life, no cyanopsia, can be taken on empty or full stomach (others better on empty stomach)
  - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis once erect
  - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra
- invasive
  - intracavernous vasodilator injection/self-injection
    - triple therapy (papaverine, phenolamine, PGE1) or PGE1 alone
    - complications: priapism (overdose), thickening of tunica albuginea at site of repeated injections (Peyronie's plaque) and hematoma
- surgical
  - penile implant (last resort): malleable or inflatable
  - penile artery reconstruction (in young men with isolated vascular lesion – investigational)

Trauma
- see Emergency Medicine, ER14

Renal Trauma

Classification According to Severity
- minor
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
- major
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

Etiology
- 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

Clinical Features
- mechanism of injury raises suspicion
- can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
- upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

Investigations
- U/A
  - hematuria: requires workup but degree does not correlate with the severity of injury
- imaging
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

Staging (Does Not Necessarily Correlate Well with Clinical Status)
- I: contusion/hematoma
- II: <1 cm laceration without urinary extravasation
- III: >1 cm laceration without urinary extravasation
- IV: urinary extravasation
- V: shattered kidney or avulsion of pedicle
Treatment
- microscopic hematuria + isolated well-staged minor injuries → no hospitalization
- gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
- surgical intervention/minimally invasive angiography and embolization:
  - absolute indications
    - hemorrhage and hemodynamic instability
  - relative indications
    - non-viable tissue and major laceration
    - urinary extravasation
    - vascular injury
    - expanding or pulsating peri-renal mass
    - laparotomy for associated injury
- follow-up with U/S or CT before d/c, and at 6 wk

Complications
- HTN in 5% of renal trauma

Bladder Trauma

Classification
- contusions: no urinary extravasation, damage to mucosa or muscularis
- intraperitoneal ruptures: often involve the bladder dome
- extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

Etiology
- blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
- blunt trauma is associated with pelvic fracture in 97% of cases

Clinical Features
- abdominal tenderness, distention, peritonitis, and inability to void
- can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
- suprapubic pain

Investigations
- U/A: gross hematuria in 90%
- imaging (including CT cystogram and post-drainage films for extravasation)

Treatment
- penetrating trauma → surgical exploration
- contusion → urethral catheter until hematuria completely resolves
- extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  - surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
- intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications
- complications of bladder injury itself are rare
- mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

Urethral Injuries

Etiology
- posterior urethra
  - common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  - shearing force on fixed membranous and mobile prostatic urethra
- anterior urethra
  - straddle injury can crush bulbous urethra against pubic rami
- other causes
  - iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
- always look for associated bladder rupture

All patients with suspected urethral injury should undergo RUG
Clinical Features
- blood at urethral meatus
- high-riding prostate on DRE
- swelling and butterfly perineal hematoma
- penile and/or scrotal hematoma
- sensation of voiding without U/O
- distended bladder

Investigations
- must perform RUG or cystoscopy prior to catheterization

Treatment
- simple contusions
  - no treatment
- partial urethral disruption
  - very gentle attempt at catheterization by urologist
  - with no resistance to catheterization → Foley x 2-3 wk
  - with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment in OR
- periodic flow rates/urethrograms to evaluate for stricture formation
- complete disruption
  - immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

Complications
- stricture

Infertility

Definition
- failure to conceive after one year of unprotected, properly timed intercourse
- incidence
  - 15% of all couples
  - ~ 35-40% female, 20% male, 25-30% combined problem

Female Factors
- see Gynecology, GY20

Male Factors

Male Reproduction
- hypothalamic-pituitary-testicular axis (HPTA)
  - pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  - LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  - FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  - FSH and testosterone support germ cells (responsible for spermatogenesis)
  - sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

Etiology
- idiopathic (40-50% infertile males)
- testicular
  - varicocele (35-40% infertile males)
  - tumor
  - congenital (Klinefelter’s triad: small, firm testes, gynecomastia, and azospermia)
  - post-infectious (epididymo-orchitis, STDs, mumps)
  - uncorrected torsion
  - cryptorchidism (<5% of cases)
- obstructive
  - iatrogenic (surgery: see below)
  - infectious (gonorrhea, chlamydia)
  - trauma
  - congenital (absence of vas deferens, CF)
- bilateral ejaculatory duct obstruction, epididymal obstructions
- Kartagener’s syndrome (autosomal recessive disorder causing defect in action of cilia)
- endocrine (see Endocrinology, E47)
- HPTA (2-3%) e.g. Kallmann’s syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
- other
  - retrograde ejaculation secondary to surgery
  - medications
  - drugs: marijuana, cocaine, tobacco, alcohol
  - increased testicular temperature (sauna, hot baths, tight pants or underwear)
  - chronic disease: e.g. liver, renal
  - unexplained infertility

**History**
- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STDs, cryptorchidism
- surgical: vasectomy, herniorrhaphy, orchidopexy, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/jaculatoin, timing, frequency
- family Hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social hx: alcohol, tobacco, cocaine, marijuana
- occupational exposures: radiation, heavy metals

**Physical Exam**
- general appearance: sexual development, gynecomastia, obesity
- scrotal exam: size, consistency, and nodularity of testicles; palpation of cord for presence of vas deferens; DRE; Valsalva for varicocele

**Investigations**
- semen analysis (SA) at least 2 specimens, collected 1-2 wk apart
  - delivery to lab within 1 h, 2-7 d of abstinence prior to collection
- hormonal evaluation
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation
  - chromosomal studies (Klinefelter’s syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

**Treatment**
- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E48)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections
- surgical
  - varicocelectomy (if indicated)
  - vasovasostomy (vasectomy reversal) or epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART)
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - in vitro fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

**WHO Guidelines**
- Normal Semen Values
  - Volume: 2-5 mL
  - Concentration: >15 million sperm/mL
  - Morphology: 30% normal forms
  - Motility: >60% adequate forward progression
  - Liquefaction: complete in 20 min
  - pH: 7.2-7.8
  - WBC: <10/HPF or <10^6 WBC/mL semen

**Mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene is associated with congenital bilateral absence of vas deferens and epididymal cysts, even if patient manifests no symptoms of CF**

**Common Terminology on SA**
- Teratospermia: Abnormal morphology
- Asthenospermia: Abnormal motility
- Oligospermia: Decreased sperm count
- Azoospermia: Absent sperm in semen
- Mixed types, i.e. oligoasthenospermia
Figure 15. Infertility workup

**Pediatric Urology**

**Congenital Abnormalities**

- not uncommon; 1/200 have congenital abnormalities of the GU tract
- six common presentations of congenital urological abnormalities

1. **ANTENATAL HYDRONEPHROSIS**

**Epidemiology**
- 1-5% fetal U/S, detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

**Differential Diagnosis**
- UPJ or UVJ obstruction
- multi-cystic dysplastic kidney
- VUR
- PUVs (only in boys)
- duplication anomalies
- ureterocele
- ectopic ureter

**Treatment**
- antenatal *in utero* intervention rarely indicated unless evidence of PUVs with oligohydramnios

2. **POSTERIOR URETHRAL VALVES**

**Epidemiology**
- the most common congenital obstructive urethral lesion in male infants

**Pathophysiology**
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

**Clinical Presentation**
- dependent on age
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive

> Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life.
• toddlers: UTIs or voiding dysfunction
• school-aged boys: voiding dysfunction → urinary incontinence
• associated findings include renal dysplasia and secondary VUR

Investigations
• most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened bladder, dilated posterior urethra (‘keyhole sign’), oligohydramnios in a male fetus
• VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

Treatment
• immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
• if resection of PUV is not possible, vescicostomy is indicated

3. URETEROPELVIC JUNCTION OBSTRUCTION

Etiology
• unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, stenosis, strictures, aberrant blood vessels
• can rarely be secondary to tumor, stone, etc. in children

Epidemiology
• the most common congenital defect of the ureter
• M:F = 2:1
• up to 40% bilateral, which may be associated with worse prognosis

Clinical Presentation
• symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
• infants: abdominal mass, urinary infection
• children: pain, vomiting, failure to thrive
• some cases are diagnosed after puberty and into adulthood
• in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl’s crisis)

Investigations
• antenatal U/S most common, Doppler U/S (rare), IVP (rare), and renal scan ± furosemide

Treatment
• surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

4. VESICOURETERAL REFLUX

Definition
• retrograde passage of urine from the bladder, through the UVJ, into the ureter

Classification
• primary reflux: incompetent or inadequate closure of UVJ
• lateral ureteral insertion, short submucosal segment
• secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
• often associated with anatomic (PUV) or functional (neuropathic) bladder obstruction

Epidemiology
• estimated ~1% of newborns, but not well known
• incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
• risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition

Investigations
• focused Hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
• also screen for signs of infection (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
• initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to high incidence of renal scarring
• height, weight, blood pressure
• Cr
- U/A, C&S
- renal U/S
- DMSA renal scan if at high risk (greater sensitivity in detecting structural defects associated with dysplasia, renal scarring or pyelonephritis; entails radiation exposure)
- family screening is controversial

**Treatment**
- spontaneous resolution in 60% of primary reflux
  - in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment and monitoring
- medical treatment: daily ABx prophylaxis at half the treatment dose for acute infection (see Table 8, U12 - TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
- surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (Deflux® or Macroplastique®)
  - indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

5. **HYPOSPADIAS**

**Definition**
- a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
- depending on severity, may result in difficulty directing urinary stream, having intercourse or depositing sperm in vagina

**Epidemiology**
- very common; 1/300 live male births
- distal hypospadias more common than proximal
- white >> black
- may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia

**Treatment**
- early surgical correction; optimal repair before 2 yr
- neonatal circumcision should be deferred because the foreskin may be utilized in the correction

6. **EPISPADIAS-EXSTROPHY COMPLEX**

**Definition**
- a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  - bladder exstrophy: congenital absence of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  - cloacal exstrophy
    - exposed bladder and bowel with imperforate anus
    - associated with spina bifida in >50%
  - epispadias (least severe)
    - urethra opens on dorsal aspect of the penis, often associated with penile curvature

**Etiology**
- represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

**Epidemiology**
- rare: incidence 1/30,000, M:F = 3:1 predominance
- high morbidity → multiple reconstructive surgeries, incontinence, infertility, reflux

**Treatment**
- surgical correction at birth
- later corrections for incontinence, VUR, and low bladder capacity may be needed
**Nephroblastoma (Wilms’ Tumor)**

**Etiology**
- arises from abnormal proliferation of metanephric blastema

**Epidemiology**
- 5% of all childhood cancers, 5% bilateral
- most common primary malignant renal tumor of childhood
- average age of incidence is 3 yr

**Clinical Features**
- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness
- microscopic hematuria
- nausea/vomiting

**Treatment**
- always investigate contralateral kidney and renal vein (for tumor thrombus)
- unilateral disease: radical nephrectomy ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

**Prognosis**
- 5 yr survival 80%

---

**Cryptorchidism/Ectopic Testes**

**Definition**
- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- ectopic testis (testis found outside its normal path of descent) is most commonly located within a superficial pouch between the external oblique fascia and Scarpa’s fascia (Denis Browne pouch)
- differential diagnosis
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

**Epidemiology**
- 2.7% of full term newborns
- 0.7-0.8% at 1 yr old

**Treatment**
- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

**Prognosis**
- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility
  - paternity rates: 53%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intraabdominal > inguinal
- surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)

---

**Disorders of Sexual Differentiation**

**Definition**
- formerly known as intersex disorders
- abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females
- considered a social emergency

**Classification**
1. 46 XY DSD
   - defect in testicular synthesis of androgens
   - androgen resistance in target tissues
   - palpable gonad

2. 46 XX DSD
   - defect in internal differentiation of gonads
   - normal testes - ovarian tissue

3. Disorders of genital development
   - hypospadias
   - ambiguous genitalia

A phenotypic male newborn with bilateral non-palpable testicles should be considered 46XX with salt-wasting CAH and must undergo proper evaluation prior to discharge.
2. 46 XX DSD
   - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
   - undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)

3. ovotesticular DSD

4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   - presence of Y chromosome → partial testis determination to varying degrees

**Diagnosis**
- thorough family Hx noting any consanguinity
- maternal Hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
- P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
- laboratory tests
  - plasma 17-OH-progesterone (after 36 h of life) → increased in 21-hydroxylase deficiency (CAH)
  - plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  - basal adrenal steroid levels
  - serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/d for 4 d)
  - serum electrolytes
  - chromosomal evaluation including sex karyotype
- U/S of adrenals, gonads, uterus, and fallopian tubes
- endoscopy and genitography of urogenital sinus

**Treatment**
- steroid supplementation as indicated (e.g. CAH)
- sex assignment after extensive family consultation
  - must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
- reconstruction of external genitalia between 6 and 12 mo
- long-term psychological guidance and support for both patient and family

**Enuresis**
- see Pediatrics, P9

**Selected Urological Procedures**

**Bladder Catheterization**
- catheter size measured by the French (Fr) scale – circumference in mm
- each 1 mm increase in diameter = approximately 3 Fr increase (standard size 16-18 Fr)
- should be removed as soon as possible to reduce the risk of UTI

**Continuous Catheterization**
- indications
  - accurate monitoring of U/O
  - relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  - temporary therapy for urinary incontinence
  - perineal wounds
  - clot prevention (24-28 Fr) for CBI
  - post-operative

**Alternatives to Continuous Catheterization**
- intermittent catheterization
- PVR measurement
- to obtain sterile diagnostic specimens for U/A, urine C&S
- management of neurogenic bladder or chronic urinary retention
- condom catheter
- suprapubic catheter

**Causes of Difficult Catheterizations and Treatment**
- patient discomfort → use sufficient lubrication (± xylocaine)
- collapsing catheter → lubrication as above ± firmer or larger catheter (silastic catheter)
• meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
• BPH → use coudé catheter as angled tip can help navigate around enlarged prostate
• urethral disruption/obstruction → filiform and followers or suprapubic catheterization
• anxious patient → anxiolytic medication

Complications of Catheterization
• infection: UTI
• meatal/urethral trauma

Contraindications
• urethral trauma: blood at the meatus of the urethra, scrotal hematoma, pelvic fracture, and/or high riding prostate

Circumcision

Definition
• removal of some or all of the foreskin from the penis

Epidemiology
• 30% worldwide
• frequency varies depending on geographic location, religious affiliation, socioeconomic classification

Medical Indications
• phimosis and recurrent paraphimosis
• recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
• balanitis xerotica obliterans or other chronic inflammatory conditions

Contraindications
• unstable or sick infant
• congenital genital abnormalities (hypospadias)
• family Hx of bleeding disorders warrants laboratory investigation prior to circumcision

Complications
• bleeding
• infection
• penile entrapment, skin bridges
• fistula
• glans injury
• penile sensation deficits

Cystoscopy

Objective
• endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
• scopes can be flexible or rigid

Indications
• gross hematuria
• LUTS (storage or voiding)
• urethral and bladder neck strictures
• bladder stones
• bladder tumor surveillance
• evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

Complications
• during procedure
  ▪ bleeding
  ▪ anesthetic-related
  ▪ perforation (rare)
• post-procedure (short-term)
  ▪ infections, e.g. epididymo-orchitis (rare)
  ▪ urinary retention
• post-procedure (long-term)
  ▪ stricture
Radical Prostatectomy

Objective
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also partially or completely removed

Indications
- treatment for localized prostate cancer

Complications
- immediate (intraoperative)
  - blood loss
  - rectal injury (extremely rare)
  - ureteral injury (extremely rare)
- perioperative
  - lymphocele formation
- late
  - moderate to severe urinary incontinence (3-10%)
  - mild urinary incontinence (≤20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumor)

Transurethral Resection of the Prostate

Objective
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination

Indications
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

Complications
- acute
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called “post-TURP syndrome”)
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinuses, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture


Study: A systematic review to compare perioperative outcomes, positive surgical margin (PSM) rates, and functional outcomes in retropubic radical prostatectomy (RRP), laparoscopic RP (LRP), and robot-assisted radical prostatectomy (RARP).

Methods: Medline database was searched. Weighted means (based on number of participants in each study) were calculated for all outcomes. Results: 58 articles were reviewed. LRP and RARP were associated with better perioperative outcomes compared to RRP. RRP, LRP, and RARP had similar post-operative complication rates ranging from 10.3-10.98%. RARP had a lower overall PSM rate than LRP and RRP. RARP had the highest continence rate and mean potency rates.

Conclusion: In high-volume centers, RRP, LRP, and RARP are safe options for treating patients with localized prostate cancer. LRP and RARP are associated with better perioperative outcomes and RARP showed lower PSM rates, higher potency and continence compared to RRP and LRP.
Extracorporeal Shock Wave Lithotripsy

Objective
• to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
• shockwaves are generated and focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications
• potential first-line therapy for renal and ureteral calculi <2.5 cm
• individuals with calculi in solitary kidney
• individuals with HTN, DM or renal insufficiency
* patient preference and wait-times play a large role in stone management

Contraindications
• acute UTI or urosepsis
• bleeding disorder or coagulopathy
• pregnancy
• obstruction distal to stone

Complications
• bacteriuria
• bacteremia
• post-procedure hematuria
• ureteric obstruction (by stone fragments)
• peri-nephric hematoma

Common Medications

Table 26. Erectile Dysfunction Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil</td>
<td>Phosphodiesterase 5 inhibitor</td>
<td>Selective inhibition of PDE5 (enzyme which degrades cGMP) Leads to sinusoidal smooth muscle relaxation and erection</td>
<td>Severe hypotension (very rare) Contraindicated if hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease)</td>
</tr>
<tr>
<td>tadalafil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vardenafil (PDE5s for use when some erection present)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alprostadil (MUSE®), PGE1 + phenolamine + papaverine mixture</td>
<td>Prostaglandin E1</td>
<td>Activation of cAMP, relaxing sinusoidal smooth muscle Local release (capsule inserted into urethra)</td>
<td>Penile pain Presyncope</td>
</tr>
<tr>
<td>triple therapy also used: papaverine, phenolamine, PGE1</td>
<td>See above</td>
<td>See above</td>
<td>Thickening of tunica albuginea at site of repeated injections (Peyronie’s plaque) Painful erection Hematoma Contraindicated if hx of priapism, or in conditions predisposing to priapism</td>
</tr>
</tbody>
</table>

Table 27. Benign Prostatic Hyperplasia Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>terazosin</td>
<td>α1 blockers</td>
<td>α1-adrenergic antagonists reduce stromal smooth muscle tone Reduce dynamic component of bladder outlet obstruction</td>
<td>Presyncope Leg edema Retrograde ejaculation Headache Asthenia Nasal congestion</td>
</tr>
<tr>
<td>doxazosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tamsulosin</td>
<td>α1A selective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alfuzosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>silodosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>finasteride</td>
<td>5-α reductase inhibitor</td>
<td>Blocks conversion of testosterone to DHT Reduces static component of bladder outlet obstruction Reduces prostatic volume</td>
<td>Sexual dysfunction PSA decreases</td>
</tr>
<tr>
<td>dutasteride</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Table 28. Prostatic Carcinoma Medications (N>0, M>0)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>leuprolide, goserelin</td>
<td>GnRH agonist</td>
<td>Initially stimulates LH, increasing testosterone and causing &quot;flare&quot; (initially increases bone pain) Later causes low testosterone</td>
<td>Hot flashes Headache Decreased libido</td>
</tr>
<tr>
<td>*diethylstilbestrol (DES)</td>
<td>Estrogens</td>
<td>Inhibit LH and cytotoxic effect on tumor cells</td>
<td>Increased risk of cardiovascular events (no longer available commercially in North America)</td>
</tr>
<tr>
<td>*cyproterone acetate</td>
<td>Steroidal antiandrogen</td>
<td>Competes with DHT for intracellular receptors:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1. Prevent flare produced by GnRH agonist</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Use for complete androgen blockade</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. May preserve potency</td>
<td></td>
</tr>
<tr>
<td>flutamide, bicalutamide</td>
<td>Non-steroidal antiandrogen</td>
<td>As above</td>
<td>Hepatotoxic: AST/ALT monitoring</td>
</tr>
<tr>
<td>*ketoconazole, spironolactone</td>
<td>Steroidogenesis inhibitors</td>
<td>Blocks multiple enzymes in steroid pathway, including adrenal androgens</td>
<td>GI symptoms Hyperkalemia Gynecomastia</td>
</tr>
</tbody>
</table>

*Very rarely used

**Table 29. Continence Agents and Overactive Bladder Medications**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxybutynin</td>
<td>Antispasmodic</td>
<td>Inhibits action of ACh on smooth muscle Decreases frequency of uninhibited detrusor contraction Diminishes initial urge to void</td>
<td>Overactive bladder Urge incontinence + urgency + frequency</td>
<td>Dry mouth Blurred vision Supraventricular tachycardia</td>
</tr>
<tr>
<td>oxybutynin, tolterodine, trospium, solifenacin, darifenacin fesoterodine</td>
<td>Anticholinergic</td>
<td>Muscarinic receptor antagonist Selective for bladder Increases bladder volume Decreases detrusor pressure</td>
<td>Overactive bladder Urge incontinence + urgency + frequency</td>
<td>As above</td>
</tr>
<tr>
<td>mirabegron</td>
<td>β3 agonist</td>
<td>Beta sympathetic receptor blocker in the bladder; relaxes bladder during storage phase</td>
<td>Overactive bladder Urge incontinence + urgency + frequency</td>
<td>Blood pressure should be monitored</td>
</tr>
<tr>
<td>imipramine</td>
<td>Tricyclic antidepressant</td>
<td>Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation</td>
<td>Stress and urge incontinence As above Weight gain Orthostatic hypotension Prolonged PR interval</td>
<td></td>
</tr>
</tbody>
</table>

Note: All anti-cholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long-acting formulations are lacking.

**References**


**Common Presenting Problems**


**Benign Renal Neoplasm**

Acronyms

Vascular Surgery

Caleb CJ Zavitz, chapter editor  
Khaled Ramadan, Karim Virani, and Vahagn Karapetyan, associate editors  
Alexa Bramall, EBM editor  
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Acronyms

Vascular Disease

Peripheral Arterial Disease

Peripheral Vascular Anatomy
Acute Arterial Occlusion/Insufficiency  
Chronic Arterial Occlusion/Insufficiency

Aortic Disease

Aortic Anatomy  
Aortic Dissection  
Aortic Aneurysm

Peripheral Venous Disease

Deep Venous Thromboembolism  
Superficial Venous Thrombosis  
Varicose Veins  
Chronic Venous Insufficiency

Carotid Stenosis  
Lymphedema

References

AAA abdominal aortic aneurysm  
ABI ankle-brachial index  
ACB angiotensin converting enzyme inhibitor  
Afib atrial fibrillation  
AKA above-knee amputation  
AKI acute kidney injury  
apTT activated partial thromboplastin time (i.e. PTT)  
ASA acetylsalicylic acid (Aspirin®)  
AT anterior tibial artery  
BKA below-knee amputation  
BP blood pressure  
CABG coronary artery bypass graft  
CAD coronary artery disease  
CBC complete blood count  
CCB calcium channel blocker  
CLU critical limb ischemia  
CTA computed tomography angiography  
CVD cerebrovascular disease  
CV chronic venous insufficiency  
CXR chest x-ray  
DIC disseminated intravascular coagulation  
DM diabetes mellitus  
DVT deep vein thrombosis  
ECASA enteric coated ASA  
ECG electrocardiogram  
Echo echocardiogram  
ET essential thrombocytemia  
EVAR endovascular aortic aneurysm repair  
EVLT endovenous laser therapy  
GSD greater saphenous vein  
HITT heparin-induced thrombocytopenia with thrombosis  
HIT hypertension  
HTN hypertensive  
IBD inflammatory bowel disease  
INR international normalized ratio  
LMWH low molecular weight heparin  
LSV lesser saphenous vein  
MCA middle cerebral artery  
MRA magnetic resonance angiography  
MSK musculoskeletal  
OCP oral contraceptive pill  
PE pulmonary embolism  
PT prothrombin time  
PIT partial thromboplastin time (i.e. aPTT)  
PVD peripheral vascular disease  
RIND reversible ischemic neurologic deficit  
SFA superficial femoral artery  
SVA superficial venous thrombosis  
TAA thoracic aortic aneurysm  
TEE transesophageal echocardiography  
TEVAR thoracic endovascular aortic aneurysm repair  
TIA transient ischemic attack  
TTE transesophageal echocardiography
VASCULAR DISEASE


Peripheral Arterial Disease

Peripheral Vascular Anatomy

- see Figure 1

Acute Arterial Occlusion/Insufficiency

Definition
- acute occlusion/rupture of a peripheral artery, usually without a history of claudication
- urgent management required: treat within 6 h or irreversible ischemia and myonecrosis may result. Exception is in acute-on-chronic occlusion, because the buildup of collaterals allows time to investigate
- tends to be lower extremity > upper extremity; femoropopliteal > aortoiliac
- etiology embolic vs. thrombotic

Etiology and Risk Factors

Table 1. Clinical Categories of Acute Limb Ischemia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>Sensory loss</th>
<th>Motor Deficit</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Viable</td>
<td>None</td>
<td>None</td>
<td>No immediate threat</td>
</tr>
<tr>
<td>IIA</td>
<td>Marginally threatened</td>
<td>None or minimal (toes)</td>
<td>None</td>
<td>Salvageable if promptly treated</td>
</tr>
<tr>
<td>IIB</td>
<td>Immediately threatened</td>
<td>More than toes</td>
<td>Mild/moderate</td>
<td>Salvageable if promptly revascularized</td>
</tr>
<tr>
<td>III</td>
<td>Irreversible</td>
<td>Profound, anesthetic</td>
<td>Profound, paralysis (rigor)</td>
<td>Major tissue loss, Amputation, Permanent nerve damage inevitable</td>
</tr>
</tbody>
</table>

Pro-Embolic States
- cardiac arrhythmias (AFib)
- endocarditis
- aneurysms

Hypercoagulable States
- congenital
  - group I (reduced anticoagulants): anti-thrombin, protein C, protein S
  - group II: factor V Leiden, prothrombin, factor VIII, hyper-homocysteinemia
- acquired (increased coagulants): immobility, cancer, pregnancy/OCP, anti-phospholipid antibody syndrome, inflammatory disorders (e.g. IBD), myeloproliferative disorders (e.g. ET), nephrotic syndrome (acquired deficit in protein C and S), disseminated intravascular coagulation (DIC), heparin-induced thrombocytopenia with thrombosis (HITT)
- for presentation of embolus vs. thrombus (see Table 2)

Investigations
- history and physical exam: depending on degree of ischemia may have to forego investigations and go straight to OR
- ABI: extension of physical exam, easily performed at bedside
- ECG, troponin: rule out recent MI or arrhythmia
- CBC: rule out leukocytosis, thrombocytosis or recent drop in platelets in patients receiving heparin
- PT/INR: patient anticoagulated/sub-therapeutic INR
- Echo: identify wall motion abnormalities, intracardiac thrombus, valvular disease, aortic dissection (type A)
- CT angiogram: underlying atherosclerosis, aneurysm, aortic dissection
- conventional catheter based angiography: can be obtained in OR; prelude to thrombolitics

Figure 1. Peripheral vascular anatomy

© Melanie Burger 2012

1. Abdominal aorta
2. Common iliac
3. External iliac
4. Internal iliac
5. Femoral
6. Femoral profunda
7. Popliteal
8. Anterior tibial
9. Tibioperoneal trunk
10. Posterior tibial
11. Peroneal
12. Dorsalis pedis

Hypercoagulable State

Congenital
- Group I (reduced anticoagulants)
  - Anti-thrombin
  - Protein C
  - Protein S
- Group II (increased coagulants)
  - Factor V Leiden
  - Prothrombin
  - Factor VIII
  - Hyper-homocysteinemia

Acquired
- Immobility
- Cancer
- Pregnancy/Systemic hormonal contraceptives/HRT
- Antiphospholipid antibody syndrome
- Inflammatory disorders (e.g. IBD)
- Myeloproliferative disorders (e.g. ET)
- Nephrotic syndrome (acquired deficit in Protein C and S)
- DIC
- HITT
Treatment
- immediate heparinization with 5000 IU bolus and continuous infusion to maintain PTT >60 s
- if impaired neurovascular status: emergent revascularization
- if intact neurovascular status: time for workup (including angiogram)
- definitive treatment
  - embolus: embolectomy
  - thrombus: thrombectomy ± bypass graft ± endovascular therapy
  - irreversible ischemia (complete loss of power or sensation, absent venous and arterial dopplers, rigor): primary amputation
- identify and treat underlying cause
- continue heparin post-operative, start warfarin post-operative day 1 x 3 mo depending on underlying etiology

Table 2. Arterial Embolism vs. Thrombosis

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Embolus</th>
<th>Thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Progressive, acute-on-chronic</td>
</tr>
<tr>
<td>Loss of function/sensation</td>
<td>Prominent</td>
<td>Less profound (due to underlying collaterals)</td>
</tr>
<tr>
<td>Hx of claudication</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Atrophic changes</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Contralateral limb pulses</td>
<td>Classically normal</td>
<td>Decreased or absent</td>
</tr>
</tbody>
</table>

Complications
- compartment syndrome with prolonged ischemia; requires 4-compartment (anterior/lateral/superficial and deep posterior) fasciotomy
- risk of arrhythmia and death with reperfusion injury
- renal failure and multi-organ failure due to toxic metabolites from ischemic muscle

Prognosis
- 12-15% mortality rate
- 5-40% morbidity rate (amputation)

Chronic Arterial Occlusion/Insufficiency

Etiology
- predominantly due to atherosclerosis; primarily lower extremities

Risk Factors
- major: smoking, DM
- minor: HTN, hyperlipidemia, family history, obesity, sedentary lifestyle, PMHx or FMHx CAD/CVD

Clinical Features
- claudication
  1. pain with exertion: usually in calves or any exercising muscle group
  2. relieved by short rest: 2-5 min, and no postural changes necessary
  3. reproducible: same distance to elicit pain, same location of pain, same amount of rest to relieve pain
- critical limb ischemia (CLI)
  1. includes rest pain, night pain, tissue loss (ulceration or gangrene)
  2. pain most commonly over the forefoot, waking person from sleep, and often relieved by hanging foot off bed
  3. ankle pressure <40 mmHg, toe pressure <30 mmHg, ABI <0.40
- pulses may be absent at some locations, bruits may be present
- signs of poor perfusion: hair loss, hypertrophic nails, atrophic muscle, skin ulcerations and infections, slow capillary refill, prolonged pallor with elevation and rubor on dependency, venous troughing (collapse of superficial veins of foot)
- other manifestations of atherosclerosis: CVD, CAD, impotence, splanchinic ischemia

Investigations
- non-invasive
  - routine blood work, fasting metabolic profile
  - ABI: take highest brachial and highest ankle (dorsalis pedis artery or posterior tibial artery) pressures for each side generally
    - ABI <0.90 abnormal, rest pain appears at <0.30 (see Table 3)
- CTA and MRA: excellent for large arteries (aorta, iliac, femoral, popliteal), may have difficulty with tibial arteries (especially in the presence of disease). Both require IV injection of nephrotoxic contrast (iodinated contrast for CT, gadolinium for MR)
- invasive
  - arteriography: superior resolution to CTA/MRA, better for tibial arteries, can be done intraoperatively

### Table 3. Ankle-Brachial Indices

<table>
<thead>
<tr>
<th>ABI Recording</th>
<th>Degree of Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.20</td>
<td>Suspect wall calcification (most common in diabetics)</td>
</tr>
<tr>
<td>&gt;0.95</td>
<td>Normal/no ischemia</td>
</tr>
<tr>
<td>0.50-0.80</td>
<td>Claudication range</td>
</tr>
<tr>
<td>&lt;0.40</td>
<td>Possible critical ischemia</td>
</tr>
</tbody>
</table>

**Treatment**
- conservative
  - risk factor modification (smoking cessation, Hba1c control, treatment of HTN (ACEI), hyperlipidemia (statin), antiplatelet therapy (ECASA))
  - exercise program (30 min 3 times per wk): improves collateral circulation, oxygen extraction at the muscle level
  - foot care (especially in DM): keep wounds clean/dry, avoid trauma and pressure on wounds
- pharmacotherapy
  - antiplatelet agents (e.g. ECASA, clopidogrel)
  - cilostazol (cAMP-phosphodiesterase inhibitor with antiplatelet and vasodilatory effects): improves walking distance for some patients with claudication
- surgical/endovascular
  - indications: severe lifestyle impairment, vocational impairment, critical ischemia
  - surgical options
    - endovascular (stenting/angioplasty)
    - endarterectomy: removal of plaque and repair with patch (usually distal aorta or common/profunda femoral)
    - bypass graft sites: aortofemoral, axillofemoral, femoropopliteal, distal arterial
      - graft choices: vein graft (reversed or in situ), synthetic (polytetrafluoroethylene graft (e.g. Gore-Tex®) or Dacron®)
    - chemical sympathectomy: sympathetic plexus destroyed with EtOH injection into nerve plexus, may stimulate vasodilation (rarely effective)
    - amputation: if not suitable for revascularization, persistent serious infections/gangrene

**Prognosis**
- claudication: conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 yr, <4% will require amputation
- for patients with CLI (rest pain, night pain, ulceration or gangrene): high risk of limb loss (which carries 25% risk of death at 1 yr)

![Figure 2. Treatment options for CLI](image-url)
Aortic Disease


Aortic Anatomy

- see Figure 3

Aortic Dissection

Definition
- tear in aortic intima allowing blood to dissect into the media
- Stanford classification: Type A (involve the ascending aorta) vs. Type B (do not)
- DeBakey Classification: Type I (involves the ascending aorta, aortic arch, and descending aorta), Type II (confined to the ascending aorta) and Type III (confined to the descending aorta distal to the left subclavian artery)
- acute <2 wk (initial mortality 1% per hour for type A dissections)
- chronic >2 wk (mortality levels up to 75-80%)

Etiology
- most common: HTN → degenerative/cystic changes → damage to aortic media
- other: connective tissue disease (e.g. Marfan’s, Ehlers-Danlos), cystic medial necrosis, atherosclerosis, congenital conditions (e.g. coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection (e.g. syphilis), trauma, arteritis (e.g. Takayasu’s)

Epidemiology
- incidence of 5.2 in 1,000,000
- M:F = 3.2:1
- small increased incidence in African-Americans (related to higher incidence of HTN)
- lowest incidence in Asians
- peak incidence 50-65 yr old; 20-40 yr old with connective tissue diseases

Clinical Features
- sudden onset tearing chest pain that radiates to back with:
  - HTN (75-85% of patients)
  - asymmetric BPs and pulses between arms (>30 mmHg difference indicates poor prognosis)
  - ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotids (ischemic stroke, Horner’s syndrome), splanchnic (mesenteric ischemia), renal (AKI), peripheral (ischemic leg), intercostal vessels (spinal cord ischemia)
  - “unseating” of aortic valve cusps (new diastolic murmur in 20-30%) in Type A dissection
  - rupture into pleura (dyspnea, hemoptyosis) or peritoneum (hypotension, shock) or pericardium (cardiac tamponade)
  - syncope

Investigations
- CXR
  - pleural cap (pleural effusion in lung apices)
  - widened mediastinum
  - left pleural effusion with extravasation of blood
- TEE: can visualize aortic valve and thoracic aorta but not abdominal aorta
- ECG: LVH ± ischemic changes, pericarditis, heart block
- CT (gold standard), aortography, MRA: 100% sensitive and specific
- blood work: lactate (rule out ischemic gut), amylase (rule out pancreatitis), troponin (rule out MI)

Treatment
- pharmacologic
  - β-blocker to lower BP and decrease cardiac contractility
  - use nifidihydropyridine CCB if there is a clear contraindication to β-blockers
  - target sBP of 110 mmHg and HR <60 bpm
  - ACEI and/or other vasodilators if insufficient BP or HR control
- surgical
  - urgent surgical consult if thoracic aortic dissection diagnosed or highly suspected
  - Type A to cardiac surgery, Type B to vascular surgery

Figure 3. Aortic anatomy
resection of segment with intimal tear
reconstitution of flow through true lumen
replacement of the affected aorta with prosthetic graft
correction of any predisposing factors
post-operative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
2/3 of patients die of operative or post-operative complications
Type A: requires emergent surgery with cardiopulmonary bypass
- hypothermic circulation for transverse arch dissections
- resuspension of aortic valve
- aortic valve replacement
- coronary re-implantation for aortic root involvement
initial mortality rate without surgery is 3% per h for first 24 h, 30% 1 wk, 80% 2 wk
Type B: managed medically in absence of spinal/mesenteric/limb malperfusion syndrome
<10-20% require urgent operation for complications
treatment can be surgical or endovascular
require follow-up over time to monitor for dilation
role for early endovascular intervention controversial (2013 INSTEAD trial)
with treatment, 60% 5 yr survival, 40% 10 yr survival

### Aortic Aneurysm

#### Definition of Aneurysm
- localized dilatation of an artery having a diameter at least 1.5x that of the expected normal diameter
  - true aneurysm: involving all vessel wall layers (intima, media, adventitia)
  - false aneurysm (also known as pseudo-aneurysm): disruption of the aortic wall or the anastomotic site between vessel and graft with containment of blood by a fibrous capsule made of surrounding tissue
- aneurysms can rupture, thrombose, embolize, erode, and fistulize

#### Classification
- thoracic aortic aneurysm (TAA): ascending, transverse arch, descending
- thoracoabdominal
- abdominal aortic aneurysm (AAA): 90-98% are infrarenal
  - suprarenal: involves one or more visceral arteries, but does not involve the chest
  - pararenal: renal arteries arise from aneurysmal aorta, but the SMA origin is not aneurysmal
  - juxtarenal: the renal arteries originate from normal aorta, but are immediately adjacent to aneurysmal aorta (there is no nonaneurysmal aorta distal to the origin of the renal arteries)
  - infrarenal: The aneurysm originages distal to the renal arteries (there is nonaneurysmal aorta distal to the origins of the renal arteries)

#### Etiology
- degenerative (atherosclerotic)
- traumatic
- mycotic (Salmonella, Staphylococcus, usually suprarenal aneurysms)
- connective tissue disorder (Marfan syndrome, Ehlers-Danlos syndrome)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic aneurysms are associated with bicuspid aortic valve
- risk factors: smoking, HTN, age >70, family history

#### Epidemiology
- incidence 4.7 to 31.9 per 100,000 for AAA and 5.9 per 100,000 for TAA
- high risk groups
  - ≥65 yr
  - M:F = 3.8:1
  - PVD, CAD, CVD
  - family history of AAA

#### Does This Patient have an Acute Thoracic Aortic Dissection
JAMA 2002;287:2262-2272

<table>
<thead>
<tr>
<th>LR + (95% CI)</th>
<th>LR – (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>1.6 (1.2-2.0)</td>
</tr>
<tr>
<td>Sudden onset of pain*</td>
<td>1.6 (1.0-2.4)</td>
</tr>
<tr>
<td>“Tearing” or “ripping” pain</td>
<td>1.2-11</td>
</tr>
<tr>
<td>Migratory sign</td>
<td>7.6 (0.6-1.0)</td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td></td>
</tr>
<tr>
<td>Pulse deficit*</td>
<td>5.7 (1.1-7.6) 0.7 (0.6-0.9)</td>
</tr>
<tr>
<td>Focal neurologic deficits</td>
<td>6.6-33</td>
</tr>
<tr>
<td>Diastolic murmur</td>
<td>1.4 (1.0-2.0) 0.9 (0.8-1.0)</td>
</tr>
<tr>
<td>*Combination of findings increases LR+: if no findings LR+ 0.1, if one LR+ 0.5, if two LR+ 5.3, if three LR+ 6.6</td>
<td></td>
</tr>
</tbody>
</table>

Debakey:   Type I: 50%           Type II: 35%
Stanford: Type A

Debakey: Type IIIA
Stanford: Type B

Figure 4. Classification of aortic dissection (black arrow indicates where the dissection begins)

ACC/AHA 2005 Guidelines define an AAA when the minimum AP diameter of abdominal aorta ≥3.0 cm
Clinical Features
• associated diseases: HTN, PVD, CAD, COPD, renal insufficiency
• most commonly in the abdominal aorta (50% abdominal aorta, 40% thoracic aorta, 10% ascending aorta)
• common presentation: due to acute expansion or disruption of wall
  ▪ syncope
  ▪ pain (chest, abdominal, flank, back)
  ▪ hypotension
  ▪ palpable pulsatile mass above the umbilicus, pulsatile abdominal mass in two directions (expandable)
  ▪ airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis (indicates thoracic or thoracoabdominal aortic aneurysm)
  ▪ distal pulses may be intact
• 75% asymptomatic (discovered incidentally)
• uncommon presentation
  ▪ ureteric obstruction and hydronephrosis (often with inflammatory aortic aneurysm)
  ▪ gastrointestinal bleed (duodenal mucosal hemorrhage, aortoduodenal fistula)
    • aortocaval fistula
    • distal embolization (blue toe syndrome)

Investigations
• blood work: CBC, electrolytes, urea, creatinine, PTT, INR, type and cross
• abdominal U/S (100% sensitive, up to ±0.6 cm accuracy in size determination)
• CT (accurate visualization, size determination)
• MRI (accurate visualization, limited access)
• aortogram (only for EVAR)
• Doppler/duplex (rule out vascular tree aneurysms elsewhere, e.g. popliteal)

Treatment
• conservative
  ▪ cardiovascular risk factor reduction: smoking cessation; control of HTN, DM, and hyperlipidemia
  ▪ regular exercise
  ▪ watchful waiting, U/S every 6 mo to 3 yr depending on size and location
• surgical
  ▪ when risk of rupture greater than or equal to risk of surgery (>5.5 cm)
  ▪ risk of rupture depends on
    • size
    • family history of rupture
    • rate of enlargement (if >0.4 cm/yr): >1 cm diameter expansion per year defines "rapid expander"
    • symptoms, comorbidities (HTN, COPD, dissection), smoking
  ▪ elective AAA repair mortality 2-5% for open repair (1-2% for EVAR); elective TAA repair mortality <10% (highest with proximal aortic and thoracoabdominal repairs)
  ▪ consider revascularization for patients with symptomatic or 3-vessel CAD before elective repair of aneurysm
  ▪ indications
    • general: ruptured, symptomatic, mycotic, associated with acute Type A dissection or complicated Type B dissection or when risk of rupture is greater than risk of surgery (size >5.5 cm or >2x normal lumen size)

Risk of AAA Rupture
<table>
<thead>
<tr>
<th>Size (diameter)</th>
<th>1 yr Rupture Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4 cm</td>
<td>0%</td>
</tr>
<tr>
<td>4-4.9 cm</td>
<td>1%</td>
</tr>
<tr>
<td>5-5.9 cm</td>
<td>5-10%</td>
</tr>
<tr>
<td>6-6.9 cm</td>
<td>10-20%</td>
</tr>
<tr>
<td>7-7.9 cm</td>
<td>20-40%</td>
</tr>
</tbody>
</table>

Endoleak Types
Definition: persistent blood flow into the aneurysm sac
Type I: ineffective seal at ends of graft
Type II: backflow from collateral vessels
Type III: ineffective seal of graft joints or rupture of graft fabric
Type IV: flow through pores of graft fabric
Type V: endotension, with continued expansion of the aneurysm without apparent flow into the sac
ascending thoracic aortic aneurysms
- symptomatic, enlarging, diameter >6 cm or >2x normal lumen size, >4.5 cm and aortic regurgitation (annuloaortic ectasia); ≥4.5-5 cm in Marfan syndrome
- contraindications: life expectancy <1 yr, terminal disease (e.g. cancer), significant comorbidities (e.g. recent MI, unstable angina), decreased mental acuity, advanced age
- surgical options
  - open surgery (laparotomy or retroperitoneal) with graft replacement
    - possible complications
    - early: renal failure, spinal cord injury (paraparesis or paraplegia), impotence, arterial thrombosis, anastomotic rupture or bleeding, peripheral emboli
    - late: graft infection/thrombosis, aortoenteric fistula, anastomotic (pseudo) aneurysm
  - endovascular aneurysm repair (EVAR)
    - newer procedure; high success rates in patients with suitable anatomy and experienced centers
    - advantages: preferred to open surgery in ruptured AAA for patients with suitable anatomy, decreased morbidity and mortality, procedure time, need for transfusion, ICU admissions, length of hospitalization, and recovery time
    - disadvantages: endoleak rates as high as 20-30%, device failure increasing as longer follow-up periods are achieved, re-intervention rates 10-30%, cost-effectiveness is an issue (devices are very expensive), radiation exposure
    - complications
      - early: immediate conversion to open repair (<1%), groin hematoma, arterial thrombosis, iliac artery rupture, and thromboemboli
      - late: endoleak, severe graft kinking, migration, thrombosis, rupture of aneurysm

Peripheral Venous Disease

Deep Venous Thromboembolism
- see Hematology, H33

Superficial Venous Thrombosis

Definition
- erythema, induration, and tenderness along the superficial vein; usually spontaneous but can follow venous cannulation

Etiology
- infectious: suppurative phlebitis (complication of IV cannulation; associated with fever/chills)
- trauma
- inflammatory: varicose veins, migratory superficial thrombophlebitis, Buerger's disease, SLE
- hematologic: polycythemia, thrombocytosis
- neoplastic: occult malignancy (especially pancreatic)
- idiopathic

Clinical Features
- most common in greater saphenous vein and its tributaries
- pain and cord-like swelling along course of involved vein
- areas of induration, erythema, and tenderness correspond to dilated and often thrombosed superficial veins
- complications
  - simultaneous DVT (up to 20% of cases), PE (rare unless DVT)
  - recurrent superficial thrombophlebitis

Investigations
- non-invasive tests (e.g. Doppler) to exclude associated DVT

Treatment
- conservative
  - moist heat, compression bandages, mild analgesic, anti-inflammatory and anti-platelet (e.g. ASA), LMWH, ambulation
- surgical excision of involved vein
  - indication: failure of conservative measures (symptoms that persist over 2 wk)
  - suppurative thrombophlebitis: broad-spectrum IV antibiotics and excision

Figure 6. EVAR endoleak
### Varicose Veins

**Definition**
- Distention of tortuous superficial veins resulting from incompetent valves in the deep, superficial, or perforator systems
- Distribution: greater or short saphenous veins and tributaries

**Etiology**
- Primary varicosities: venous valve incompetence or obstruction
  - Contributing factors: increasing age, systemic hormonal contraceptive use, occupations requiring long hours of standing, pregnancy, obesity
- Secondary varicosities: DVT, malignant pelvic tumors with venous compression, congenital anomalies, arteriovenous fistulae

**Epidemiology**
- Primary varicose veins are the most common form of venous disorder of lower extremity
- 10-20% of population

**Clinical Features (Not Correlated with Varicosity Size)**
- Diffuse aching, fullness/tightness, nocturnal cramping
- Aggravated by prolonged standing (end of day), premenstrual
- Visible long, dilated and tortuous superficial veins along thigh and leg
- Ulceration, hyperpigmentation, and induration (secondary varicosities)
- Brodie-Trendelenburg test (valvular competence test)
  - With patient supine, raise leg and compress saphenous vein at thigh, have patient stand – if veins fill quickly from top down then incompetent valves; use multiple tourniquets to localize incompetent veins

**Complications**
- Recurrent superficial thrombophlebitis
- Hemorrhage: external or subcutaneous
- Ulceration, eczema, lipodermatosclerosis, and hyperpigmentation

**Treatment**
- Largely a cosmetic problem
- Conservative: elevation of leg and/or elastic compression stockings
- Surgical: high ligation and stripping of the long saphenous vein and its tributaries, ultrasound-guided foam sclerotherapy, endovenous laser therapy
- Indications for surgery: symptomatic varix (pain, bleeding, recurrent thrombophlebitis), tissue changes (hyperpigmentation, ulceration), failure of conservative treatment, cosmetics

**Prognosis**
- Benign course with predictable complications
- Almost 100% symptomatic relief with treatment if varicosities are primary
- Good cosmetic results with treatment
- Significant post-operative recurrence, especially with sclerosing agent injection

### Chronic Venous Insufficiency

**Definition**
- Venous insufficiency and skin damage

**Etiology**
- Calf muscle pump dysfunction and valvular incompetence (valvular reflux) due to phlebitis, varicosities, or DVT
- Venous obstruction

**Clinical Features**
- Pain (most common), ankle and calf edema – relieved by foot elevation
- Pruritus, brownish hyperpigmentation (hemosiderin deposits)
- Stasis dermatitis, subcutaneous fibrosis if chronic (lipodermatosclerosis)
- Ulceration: shallow, above medial malleolus, weeping (wet), painless, irregular outline
- Signs of DVT/varicose veins/thrombophlebitis

**Investigations**
- Doppler U/S (most commonly used)
- Venography (gold standard), or ambulatory venous pressure measurement (not often used)
Treatment

- **conservative**
  - elastic compression stockings, ambulation, periodic rest-elevation, avoid prolonged standing
  - ulcers: multilayer compression bandage, antibiotics PRN
  - endovenous: laser or radiofrequency ablation, or foam sclerotherapy
- **surgical**
  - if conservative measures fail, or if recurrent/large ulcers
  - surgical ligation of perforators in region of ulcer (GSV/LSV ligation and stripping)

### Carotid Stenosis

**Definition**
- narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids

**Risk Factors**
- for atherosclerosis: HTN, smoking, DM, CVD or CAD, dyslipidemia

**Clinical Features**
- may be asymptomatic
- symptomatic stenosis may present as TIA, RIND, or stroke
- retinal insufficiency or infarct permanently or temporarily (ipsilateral amaurosis fugax), (see Ophthalmology, OP37)
- MCA contralateral occlusive symptoms

**Investigations**
- CBC, PTT/INR (hypercoagulable states)
- fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)
- auscultation over carotid bifurcation for bruits (do not correlate with degree of stenosis)
- carotid duplex: determines severity of disease (mild/moderate/severe stenosis of occlusion)
- angiogram: “gold standard” but invasive and 1/200 risk of stroke (not for screening)
- MRA: safer than angiogram, may overestimate stenosis
- CTA

**Treatment**
- control of HTN, lipids, diabetes
- antiplatelet agents (ASA ± dipyridamole, clopidogrel) ~25% relative risk reduction
- carotid endarterectomy (generally if symptomatic and >70% stenosis)
- endovascular angioplasty ± stenting

**Prognosis**

**Table 4. Symptomatic Carotid Stenosis: North American Symptomatic Carotid Endarterectomy Trial (NASCET)**

<table>
<thead>
<tr>
<th>% Stenosis on Angiogram</th>
<th>Risk of Major Stroke or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical Rx</td>
</tr>
<tr>
<td>70-99%</td>
<td>26% over 2 yr</td>
</tr>
<tr>
<td>50-69%</td>
<td>22% over 5 yr</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>Surgery has no benefit with 5% complication rate</td>
</tr>
</tbody>
</table>

**Table 5. Asymptomatic Carotid Stenosis: Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST)**

<table>
<thead>
<tr>
<th>% Stenosis on Angiogram</th>
<th>Risk of Major Stroke or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical Rx</td>
</tr>
<tr>
<td>70-99%</td>
<td>26% over 2 yr</td>
</tr>
<tr>
<td>60-99%</td>
<td>11% over 5 yr</td>
</tr>
<tr>
<td>50-69%</td>
<td>11.8% over 5 yr</td>
</tr>
</tbody>
</table>

**Prevention of Disabling and Fatal Strokes by Successful Carotid Endarterectomy in Patients Without Recent Neurological Symptoms:**

**Randomized Controlled Trial**

*Lancet* 2004;363:1491-1502

Study: Asymptomatic Carotid Surgery Trial (ACST), a RCT with follow-up at 5 yr.

Patients: 3,120 asymptomatic patients with significant carotid artery stenosis were randomized equally between immediate carotid endarterectomy (CEA) and indefinite deferral of CEA and were followed for up to 5 yr (mean 3.4 yr).

Main Outcome: Any stroke (including fatal or disabling).

Conclusions: In asymptomatic patients with significant carotid artery stenosis, immediate CEA reduced the net 5 yr stroke risk from about 12% to about 6%. Half of this 5 yr benefit involved disabling or fatal strokes.
Lymphedema

Definition
- obstruction of lymphatic drainage resulting in edema with high protein content

Etiology
- primary:
  - Milroy's syndrome: congenital hereditary lymphedema
  - lymphedema praecox (75% of cases): starts in adolescence
  - lymphedema tarda: starts >35 yr
- secondary:
  - infection: filariasis (#1 cause worldwide), post-operative
  - malignant infiltration: axillary, groin or intrapelvic
  - radiation/surgery (axillary, groin lymph node removal): #1 cause in North America

Clinical Features
- classically non-pitting edema
- impaired limb mobility, discomfort/pain, psychological distress

Treatment
- avoid limb injury (can precipitate or worsen lymphedema)
- skin hygiene
  - daily skin care with moisturizers
  - topical treatment of fungal infection; systemic treatment of bacterial infection
- external support
  - intensive: compression bandages
  - maintenance: lymphedema sleeve
- exercise
  - gentle daily exercise of affected limb, gradually increasing ROM
  - must wear a compression sleeve/bandages when doing exercises
- massage and manual lymph drainage therapy

Prognosis
- if left untreated becomes resistant to treatment due to subcutaneous fibrosis
- cellulitis causes rapid increase in swelling; can lead to sepsis and death
References

Guidelines

Vascular Surgery
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Abdominal Hernia; GS22
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Abdominal Mass; GS5, P40
Abdominal Pain; ER18, ER58, FM13, GS4, P39
Abdominal Trauma; ER13
Abdominal Wall; U2
Abdominal X-Ray; M10
Abducens Nerve; N9
Abrasions; ER18
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Absolute Risk Reduction; PH10
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Accessory Nerve; N11
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Achilles Tendon Rupture; OR38
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Acid-Base Status; R5
Acidosis; R6
Acne; D11
Acneiform Eruptions; D11
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Acute Cholangitis; GS48
Acute Cholecystitis; MI15
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Acute Epiglottitis; OT45
Acute Interstitial Nephritis; NP28
Acute Kidney Injury; NP33
Acute Laryngotraechobronchitis; OT45
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Acute Lymphoblastic Leukemia; H43
Acute Myocardial Infarction; ER23
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CN V: Trigeminal Nerve; N9
CN VI: Abducens Nerve; N9
CN VII: Facial Nerve; N10
CN VIII: Vestibulocochlear Nerve; N10
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Congenital Dermal Melanocytosis; P78
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Congenital Hypothyroidism; P29
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Erythema Nodosum; D21
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