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This manual is a concise reference for the busy clinician in need of immediate medical information. Its purpose is to provide a fast and efficient way to identify important clinical, laboratory, and diagnostic imaging information.

To limit its size to a pocket reference, less emphasis has been placed on pathophysiology and epidemiology, with more emphasis on practical clinical information. Clinical algorithms and tables have been used extensively throughout the manual to simplify difficult topics and to enhance recollection of principal points. It is hoped that its concise style will help the reader, particularly during an active clinical service, when time to read is extremely limited.

For the 8th edition we have added color images to most of the medical disorders online to facilitate identification and understanding of these illnesses and help with Board preparation.

The combination of practical clinical information with drug therapeutics, procedures, diagnostic imaging, and laboratory medicine makes this manual unique and useful, not only to medical residents and students, but also to practicing physicians and allied health professionals. I wish to thank the many thousands of physicians who have made the prior editions a best-seller in medical publishing and hope that future users will find this edition the most useful medical handbook that they will ever purchase during their training.

Fred F. Ferri, MD, FACP

Pearls of Wisdom in Medicine

1. Common things occur commonly.
2. When you hear hoofbeats, think of horses, not zebras.
3. Place your bets on uncommon manifestations of common conditions, rather than common manifestations of uncommon conditions.
4. If what you are doing is working, keep on doing it.
5. If what you are doing is not working, stop doing it.
6. If you don’t know what to do, don’t do anything.
7. Above all, never let a surgeon get your patient.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;</td>
<td>Greater than</td>
</tr>
<tr>
<td>&lt;</td>
<td>Less than</td>
</tr>
<tr>
<td>+</td>
<td>Positive; plus</td>
</tr>
<tr>
<td>-</td>
<td>Negative</td>
</tr>
<tr>
<td>↑</td>
<td>Increase</td>
</tr>
<tr>
<td>↓</td>
<td>Decrease</td>
</tr>
<tr>
<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
</tr>
<tr>
<td>AAT</td>
<td>Alpha1-antitrypsin deficiency</td>
</tr>
<tr>
<td>Ab</td>
<td>Antibody</td>
</tr>
<tr>
<td>Abd</td>
<td>Abdomen</td>
</tr>
<tr>
<td>ABG</td>
<td>Arterial blood gas</td>
</tr>
<tr>
<td>ABI</td>
<td>Ankle-brachial index</td>
</tr>
<tr>
<td>Abnl</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Abx</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>ACA</td>
<td>Anticardiolipin antibody</td>
</tr>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACD</td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ACEI</td>
<td>ACE inhibitor</td>
</tr>
<tr>
<td>ACL</td>
<td>Anticardiolipin antibody</td>
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<tr>
<td>ACLS</td>
<td>Advanced cardiac life support</td>
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<tr>
<td>ACS</td>
<td>Acute coronary syndrome</td>
</tr>
<tr>
<td>ACT</td>
<td>Activated clotting time</td>
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<tr>
<td>ACTH</td>
<td>Adrenocorticotropic hormone</td>
</tr>
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<td>ACV</td>
<td>Assist-control ventilation</td>
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<tr>
<td>ADA</td>
<td>American Dietetic Association</td>
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<td>ADH</td>
<td>Antidiuretic hormone</td>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
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<td>ADPKD</td>
<td>Autosomal dominant polycystic kidney disease</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<tr>
<td>AFB</td>
<td>Acid-fast bacilli</td>
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<td>AFP</td>
<td>Alpha-fetoprotein</td>
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<tr>
<td>AG</td>
<td>Aminoglycoside; anion gap</td>
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<td>ACN</td>
<td>Acute glomerulonephritis</td>
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<td>AHA</td>
<td>American Heart Association</td>
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<td>AI</td>
<td>Aortic insufficiency</td>
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<td>AIDS</td>
<td>Acquired immunodeficiency syndrome</td>
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<td>AIHA</td>
<td>Autoimmune hemolytic anemia</td>
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<td>AIN</td>
<td>Acute interstitial nephritis</td>
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<td>alb</td>
<td>Albumin</td>
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<tr>
<td>alk phos</td>
<td>Alkaline phosphatase</td>
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<td>ALL</td>
<td>Acute lymphocytic leukemia</td>
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<td>ALT</td>
<td>Alanine aminotransferase</td>
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<tr>
<td>AMA</td>
<td>Against medical advice</td>
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<tr>
<td>AML</td>
<td>Acute myelogenous leukemia</td>
</tr>
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<td>ANA</td>
<td>Antinuclear antibody</td>
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<tr>
<td>ANCA</td>
<td>Antineutrophil cytoplasmic antibody</td>
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<tr>
<td>AP</td>
<td>Anteroposterior</td>
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<td>APCR</td>
<td>Activated protein C resistance</td>
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<td>APS</td>
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<td>Activated partial thromboplastin time</td>
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<td>AR</td>
<td>Atrial regurgitation</td>
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<td>ARB</td>
<td>Angiotensin receptor blocker</td>
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<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
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<td>ARF</td>
<td>Acute renal failure</td>
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<td>AS</td>
<td>Aortic stenosis</td>
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<td>ASA</td>
<td>Aspirin</td>
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<td>ASD</td>
<td>Atrial septal defect</td>
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<td>ASLO</td>
<td>Antistreptolysin O</td>
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<td>ASMA</td>
<td>Anti–smooth muscle antibody</td>
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<td>AST</td>
<td>Aspartate aminotransferase</td>
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<td>ATN</td>
<td>Acute tubular necrosis</td>
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<td>AV</td>
<td>Arteriovenous; atrioventricular</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
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<tr>
<td>CVP</td>
<td>Central venous pressure</td>
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<td>CVVHD</td>
<td>Continuous venovenous hemodialysis</td>
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<td>CXR</td>
<td>Chest x-ray</td>
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<tr>
<td>D&amp;C</td>
<td>Dilation and curettage</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>d/c</td>
<td>Discharged</td>
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<tr>
<td>DFA</td>
<td>Direct fluorescent antibody</td>
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<tr>
<td>DI</td>
<td>Diabetes insipidus</td>
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<tr>
<td>DIC</td>
<td>Disseminated intravascular coagulation</td>
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<tr>
<td>diff</td>
<td>Differential</td>
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<tr>
<td>DIP</td>
<td>Distal interphalangeal</td>
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<td>DKA</td>
<td>Diabetic ketoacidosis</td>
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<td>DM</td>
<td>Diabetes mellitus</td>
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<td>DMARD</td>
<td>Disease modifying antirheumatic drug</td>
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<tr>
<td>DNR</td>
<td>Do not resuscitate</td>
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<td>DOT</td>
<td>Directly observed therapy</td>
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<td>DRE</td>
<td>Digital rectal examination</td>
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<td>DS</td>
<td>Double strength</td>
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<td>DTRs</td>
<td>Deep tendon reflexes</td>
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<td>DVT</td>
<td>Deep venous thrombosis</td>
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<td>Dx</td>
<td>Diagnosis</td>
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<td>D5W</td>
<td>Dextrose (5%) in water</td>
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<td>EA</td>
<td>Epidural abscess</td>
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<td>EBV</td>
<td>Epstein-Barr virus</td>
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<td>EC</td>
<td>Emergency contraception</td>
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<td>ECF</td>
<td>Extracellular fluid</td>
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<td>ECG</td>
<td>Electrocardiography</td>
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<td>ECM</td>
<td>Erythema chronicum migrans</td>
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<tr>
<td>EEG</td>
<td>Electroencephalography</td>
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<td>EF</td>
<td>Ejection fraction</td>
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<td>EGD</td>
<td>Esophagogastroduodenoscopy</td>
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<td>Enzyme-linked immunosorbent assay</td>
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<td>ELISA</td>
<td>Enzyme-linked immunosorbent assay</td>
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<td>Electromyography</td>
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<td>ERCP</td>
<td>Endoscopic retrograde cholangiopancreatography</td>
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<td>ESR</td>
<td>Erythrocyte sedimentation rate</td>
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<td>ESRD</td>
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<td>ET0H</td>
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<td>Growth hormone-releasing hormone</td>
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<td>HELLP</td>
<td>Hemolysis, elevated liver enzymes, and low platelet count</td>
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<tr>
<td>HGE</td>
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<td>HHS</td>
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<tr>
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<td>LAP</td>
<td>Leukocyte alkaline phosphatase</td>
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<td>Left bundle branch block</td>
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<td>Abbreviation</td>
<td>Term</td>
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<td>Lactate dehydrogenase</td>
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<td>LDL</td>
<td>Low-density lipoprotein</td>
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<td>Lower extremity</td>
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<td>LFTs</td>
<td>Liver function tests</td>
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<td>Luteinizing hormone</td>
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<td>LHRH</td>
<td>Luteinizing hormone-releasing hormone</td>
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<td>Lower motor neuron</td>
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<td>LH</td>
<td>Left ventricular hypertrophy</td>
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<tr>
<td>MAC</td>
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<td>MAOI</td>
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<td>Milliequivalent</td>
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<td>Myasthenia gravis</td>
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<td>MGUS</td>
<td>Monoclonal gammopathy of uncertain significance</td>
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<td>Minimal</td>
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<td>MRSA</td>
<td>Methicillin-resistant Staphylococcus aureus</td>
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<tr>
<td>MS</td>
<td>Mitral stenosis; multiple sclerosis</td>
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<tr>
<td>ΔMS</td>
<td>Change in mental status</td>
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<td>Methotrexate</td>
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<td>NaHCO3−</td>
<td>Bicarbonate</td>
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<td>Nerve conduction velocity</td>
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<td>Nausea and/or vomiting</td>
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<td>Overdose</td>
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<td>Ova and parasites</td>
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<td>Paco2</td>
<td>Partial pressure of CO2 in arterial blood</td>
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<tr>
<td>Pao2</td>
<td>Partial pressure of O2 in arterial blood</td>
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<tr>
<td>PA</td>
<td>Pulmonary artery; posteroanterior</td>
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<td>PAC</td>
<td>Percutaneous atrial contraction</td>
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<td>PAD</td>
<td>Peripheral arterial disease</td>
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<td>Pulmonary artery diastolic pressure</td>
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<td>Premature ventricular contraction</td>
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<td>q</td>
<td>Every</td>
</tr>
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<td>Daily</td>
</tr>
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<td>Four times daily</td>
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</tr>
<tr>
<td>r/o</td>
<td>Rule out</td>
</tr>
<tr>
<td>ROS</td>
<td>Review of systems</td>
</tr>
<tr>
<td>RP</td>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>RPGN</td>
<td>Rapidly progressive glomerulonephritis</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td>RT</td>
<td>Radiation therapy</td>
</tr>
<tr>
<td>RTA</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>RUO</td>
<td>Right upper quadrant</td>
</tr>
<tr>
<td>RV</td>
<td>Residual volume; right ventricle</td>
</tr>
<tr>
<td>RVH</td>
<td>Right ventricular hypertrophy</td>
</tr>
<tr>
<td>Rx</td>
<td>Therapy</td>
</tr>
<tr>
<td>SAH</td>
<td>Subarachnoid hemorrhage</td>
</tr>
<tr>
<td>SBP</td>
<td>Spontaneous bacterial peritonitis; systolic blood pressure</td>
</tr>
<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>SCLC</td>
<td>Small cell lung cancer</td>
</tr>
<tr>
<td>SCT</td>
<td>Stem cell transplantation</td>
</tr>
<tr>
<td>SEA</td>
<td>Spinal epidural abscess</td>
</tr>
<tr>
<td>sec</td>
<td>Second</td>
</tr>
<tr>
<td>SHx</td>
<td>Social history</td>
</tr>
<tr>
<td>SIAD</td>
<td>Syndrome of inappropriate antidiuresis</td>
</tr>
<tr>
<td>SIADH</td>
<td>Syndrome of inappropriate antidiuretic hormone</td>
</tr>
<tr>
<td>SIMV</td>
<td>Synchronized intermittent mandatory ventilation</td>
</tr>
<tr>
<td>SJS</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>SL</td>
<td>Sublingual</td>
</tr>
<tr>
<td>SLE</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Serotonin-norepinephrine reuptake inhibitors</td>
</tr>
<tr>
<td>SOB</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>SP</td>
<td>Spontaneous pneumothorax</td>
</tr>
<tr>
<td>SPEP</td>
<td>Serum protein immunoelectrophoresis</td>
</tr>
<tr>
<td>SS</td>
<td>Serotonin syndrome, Sjögren’s syndrome</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>SSS</td>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td>SESEP</td>
<td>Somatosensory evoked potential</td>
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<tr>
<td>STD</td>
<td>Sexually transmitted disease</td>
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<tr>
<td>SV</td>
<td>Stroke volume</td>
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<tr>
<td>SVC</td>
<td>Superior vena cava</td>
</tr>
<tr>
<td>SVR</td>
<td>Systemic vascular resistance</td>
</tr>
<tr>
<td>SVT</td>
<td>Supraventricular tachycardia</td>
</tr>
<tr>
<td>Sx</td>
<td>Symptoms</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TBNa</td>
<td>Total body sodium</td>
</tr>
<tr>
<td>TBW</td>
<td>Total body water</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>TGs</td>
<td>Triglycerides</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
</tr>
<tr>
<td>TIBC</td>
<td>Total iron binding capacity</td>
</tr>
<tr>
<td>tid</td>
<td>Three times daily</td>
</tr>
<tr>
<td>TIPS</td>
<td>Transjugular intrahepatic portosystemic shunt</td>
</tr>
<tr>
<td>TLC</td>
<td>Total lung capacity</td>
</tr>
<tr>
<td>TMP-SMZ</td>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>TNP</td>
<td>Tumor necrosis factor</td>
</tr>
<tr>
<td>TPN</td>
<td>Total parenteral nutrition</td>
</tr>
<tr>
<td>TR</td>
<td>Tricuspid regurgitation</td>
</tr>
<tr>
<td>TRH</td>
<td>Thyrotropin-releasing hormone</td>
</tr>
<tr>
<td>TSH</td>
<td>Thyroid-stimulating hormone</td>
</tr>
<tr>
<td>TT</td>
<td>Thrombin time</td>
</tr>
<tr>
<td>TTE</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>TTP</td>
<td>Thrombotic thrombocytopenic purpura</td>
</tr>
<tr>
<td>TSS</td>
<td>Toxic shock syndrome</td>
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<tr>
<td>TURP</td>
<td>Transurethral resection of prostate</td>
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<tr>
<td>U/A</td>
<td>Urinalysis</td>
</tr>
<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>UE</td>
<td>Upper extremity</td>
</tr>
<tr>
<td>UFH</td>
<td>Unfractionated heparin</td>
</tr>
<tr>
<td>UGI</td>
<td>Upper gastrointestinal tract</td>
</tr>
<tr>
<td>UMN</td>
<td>Upper motor neuron</td>
</tr>
<tr>
<td>URI</td>
<td>Upper respiratory infection</td>
</tr>
<tr>
<td>U/S</td>
<td>Ultrasonography</td>
</tr>
<tr>
<td>UTE</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>VAT</td>
<td>Video-assisted thoracoscopy</td>
</tr>
<tr>
<td>VATS</td>
<td>Video-assisted thoracoscopic surgery</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity</td>
</tr>
<tr>
<td>VDRL</td>
<td>Venereal Disease Research Laboratory (test for syphilis)</td>
</tr>
<tr>
<td>VEP</td>
<td>Visual evoked potential</td>
</tr>
<tr>
<td>VIP</td>
<td>Vasoactive intestinal peptide</td>
</tr>
<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>V/Q</td>
<td>Ventilation-perfusion scan</td>
</tr>
<tr>
<td>VS</td>
<td>Vital signs</td>
</tr>
<tr>
<td>VSD</td>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>VTE</td>
<td>Venous thromboembolism</td>
</tr>
<tr>
<td>vWD</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>vWF</td>
<td>von Willebrand factor</td>
</tr>
<tr>
<td>w/</td>
<td>With</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell count</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>wk</td>
<td>Week</td>
</tr>
<tr>
<td>w/o</td>
<td>Without</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff-Parkinson-White syndrome</td>
</tr>
<tr>
<td>w/u</td>
<td>Workup</td>
</tr>
<tr>
<td>w/v</td>
<td>Weight/Volume</td>
</tr>
</tbody>
</table>
THE MEDICAL HISTORY

A. Evaluating the Patient (H&P)

1. CC: reason for seeking medical attention; when possible, it should be stated in the patient’s own words.
2. HPI: chronologic narrative of the patient’s medical problems. The description of the sx should include the following: location, radiation, quality (deep, sharp, stinging), quantity or severity, timing (onset, duration, frequency), aggravating or relieving factors, associated manifestations, prior investigations, prior treatment.
3. PMHx: general state of health, significant childhood and adult illnesses, prior hospitalizations (medical, surgical).
4. Allergies: foods, drugs; describe the type of allergic reaction.
5. Current medications: dose, frequency, and duration of present drug regimen; include all nonprescription drugs and herbal products.
6. FHx: age and health status or age and cause of death of each immediate family member. Inquire about FHx of diabetes, heart disease, HTN, cancer, arthritis, mental disorder, or any hereditary conditions.
7. SHx:
   a. Lifestyle, home situation, significant others
   b. Cigarette smoking (quantity in pack years), EtOH usage, drugs
   c. Occupational hx
   d. Religious beliefs relevant to health
   e. Sexual preference (if relevant to health)
8. ROS:
   a. General: overall state of health (usual weight, recent weight change, fever, night sweats, sleeping habits, appetite)
   b. Skin: rashes, pruritus, color change, pigmentation
   c. Head: headaches, trauma
   d. Eyes: vision, visual disturbances, last eye exam
   e. Ears: hearing, tinnitus, vertigo, infections, d/c
   f. Nose and sinuses: epistaxis, nasal stuffiness, sinusitis, sense of smell
   g. Mouth and throat: condition of teeth, last dental exam, presence of sore throat or mouth lesions
   h. Neck: lumps, “swollen glands,” pain in the neck region
   i. Breast: pain, h/o lumps, bleeding, nipple d/c; if female, inquire if she performs self-exam
   j. Respiratory: cough, wheezing, sputum (quantity, color), shortness of breath, pain associated w/breathing
   k. Cardiac: chest pain, palpitations, orthopnea, edema, heart murmurs, h/o HBP
   l. GI: N/V, change in bowel habits, GI bleeding, constipation, diarrhea, abd pain, increased girth
   m. GU: dysuria, frequency, urgency, nocturia, d/c, STDs, libido, sexual problems, bleeding
n. Gyn/reproductive: age at menarche, last menstrual period, frequency and duration of menses, number and complications of pregnancies, age at menopause, contraception
o. Musculoskeletal: weakness, arthritis, gout, joint pains, swelling or stiffness, muscle cramps
p. Peripheral vascular: varicose veins, thrombophlebitis, claudication, RP
q. Neuropsychiatric: seizures, syncope, weakness, paralysis, extreme mood changes, insomnia, anxiety, psychiatric care, suicidal ideation
r. Endocrine: heat or cold intolerance, polydipsia, polyuria, polyphagia
s. Hematologic: easy bruising, transfusion reactions, excessive bleeding, h/o anemia

2 THE PHYSICAL EXAMINATION

1. VS: Record pulse, respiration, temperature, and BP (measured in both arms).
2. General description: Observe state of health, general appearance, nutritional status, body development, personal hygiene, posture, signs of anxiety, and apparent age.
3. Skin:
   a. Observe texture, color, temperature, and turgor and note any lesions.
   b. Note distribution, amount, and texture of hair.
   c. Note color of nail beds and shape of nails.
4. Lymph nodes: Note size, consistency, mobility, and tenderness of lymph nodes.
5. Head: Note size, shape, symmetry, and any unusual lesions.
6. Eyes: Note position and alignment of eyes. Inspect lacrimal glands, eyelids, cornea, sclera, and pupils; test visual fields and pupillary reactions; closely examine the fundi; observe range of eye movements, note visual field defects; assess near vision.
   **Clinical Pearl:** The Argyll Robertson pupil is a pupil constricted 1 to 2 mm that reacts to accommodation but is nonreactive to light. Classically associated with neurosyphilis, it can be seen with sarcoidosis, MS, DM, Lyme disease, CNS tumors or hemorrhage, Wernicke's encephalopathy, and other conditions associated with lesions in the area of the Edinger-Westphal nucleus. Adie's tonic pupil is a pupil dilated 3 to 6 mm that reacts closely in response to light and accommodation. It is often associated with diminished or absent DTRs. Its cause is unknown.
7. Ears: Inspect auricles, canals, and tympanic membranes; check auditory acuity by whispering in the patient's ear or by placing a watch against the patient's ear.
8. Nose and sinuses: Inspect the external nose, nasal mucosa, and septum; palpate frontal and maxillary sinuses for evidence of tenderness.
9. Mouth and throat: Inspect lips, gums, teeth, tongue, palate, and pharynx.
10. Neck:
    a. Palpate thyroid gland, inspect and palpate cervical nodes, and examine trachea.
    b. When palpating the carotid arteries, never do both simultaneously (may cause syncope).
    c. Auscultate carotids for pulses, upstroke, and presence of bruits.
    d. Note presence of JVD and angle of distention.
    e. Note range of neck movements and any nuchal rigidity.
11. Back: Inspect and palpate spine and muscles of back; note any kyphosis or scoliosis; note presence or absence of tenderness and range of motion of back.
12. Chest:
    a. Inspect, palpate, and percuss lungs.
    b. Observe respiratory movements and use of respiratory muscles.
    c. Listen to quality and intensity of breath sounds.
    d. Listen for e to change with whispered pectoriloquy (ninety-nine).
13. Heart:
   a. Inspect and palpate precordium; locate apical impulse.
   b. Using both bell and diaphragm, auscultate for S1, S2 (intensity, splitting), abnl heart sounds (S3, S4, clicks, rubs, hums, snaps), murmurs (note timing, intensity, pitch, location, radiation, quality).

14. Breasts:
   a. Inspect breasts w/patient’s arms relaxed, elevated, and then w/patient’s hands pressed against hips.
   b. Note symmetry, contour, abnl shapes, skin color, retraction, thickening, edema, venous pattern.
   c. Inspect nipples for size, shape, inversion, rashes, ulceration, d/c.
   d. Palpate for presence of masses and tenderness; feel for the presence of axillary adenopathy.

15. Abdomen:
   a. Observe skin color, contour, scars, masses, obesity, rigidity, ascites, venous pattern, and pulsatile masses.
   b. Auscultate for bowel sounds and abdominal bruits.
   c. Percuss abd and note tympany, shifting dullness, and size of liver and spleen.
   d. Note size, shape, consistency, and tenderness.

16. Rectal examination:
   a. Examine anus and rectal wall for lesions, inflammation, and sphincter tone; note any nodules or other abnormalities.
   b. Test any fecal material for occult blood.
   c. In male patients, palpate prostate and identify lateral lobes (note size, shape, and consistency of prostate).

17. Genitalia:
   a. Male
      i. Inspect distribution of pubic hair.
      ii. Examine penis (note any ulcers, nodules, scars, signs of inflammation); gently compress glans and note any d/c or tenderness.
      iii. Inspect scrotum (note any lumps, swelling, nodules, ulcers, size and shape of both testicles); transilluminate any swelling.
      iv. Inspect inguinal and femoral areas for bulges; examine patient for presence of hernias.
   b. Female
      i. Inspect external genitalia (labia clitoris, urethral orifice, vaginal opening) and note distribution of pubic hair; note any nodules, d/c, bulges, and swelling.
      ii. Perform internal examination (if indicated): insert speculum and note vaginal wall and cervical os; obtain specimen for cervical cytology; perform bimanual exam w/index and middle finger (placing the other hand above abd); identify position and mobility of cervix; note any uterine and ovarian masses, enlargement, or tenderness.
      iii. Perform rectovaginal exam; note any nodules or other lesions.

18. Inguinal area: Palpate for inguinal nodes; palpate femoral arteries (describe pulses, note any bruits).

19. Neurologic examination:
   a. Mental status and speech: check orientation, memory, and expression; check quality, quantity, and organization of speech. Consider “mini-cog exam” or “Folstein MMSE” (Table 1-3) in patients w/mental status changes or dementia.
   b. Cranial nerves
   c. Sensory: pinprick, light touch, joint position, temperature, vibration
   d. Cerebellar functions: evaluate rapid alternating hand movements, heel-to-shin, finger-to-nose, and gait.
   e. Motor: check muscle strength, muscle tone, coordination; check Romberg’s sign, reflexes, plantar responses; note any abnl reflexes.
Chapter 1  Surviving the Wards

3 THE ELDERLY PATIENT

1. Geriatric screening questions:
   a. Are you having trouble with your memory?
   b. Have you fallen in the past year?
   c. Do you have trouble hearing?
   d. Do you have trouble with your vision? Do you wear glasses?
   e. Have you lost more than 10 pounds in the past 6 months?
   f. Do you feel sad or depressed?

2. ADLs:
   a. Toileting: Do you ever lose urine when you don’t want to? Do you have difficulty getting to the bathroom?
   b. Feeding: Do you have any difficulty feeding yourself? Are you able to feed yourself? Do you eat a special diet?
   c. Dressing: Are you able to dress yourself? Do you have any difficulty with dressing?
   d. Grooming: Do you need assistance with cutting your nails, brushing your hair?
   e. Walking: How far are you able to walk?
   f. Bathing: Are you able to bathe yourself? Do you need assistance with bathing? Do you have a shower chair? Are you afraid to fall in the shower?

3. Instrumental ADLs (IADLs):
   a. Telephone: Are you able to use the telephone? Who would you call if there was an emergency? Do you have a lifeline?
   b. Shopping: Do you do your own shopping? If not, who helps you?
   c. Food preparation: Do you cook your own food? Who prepares or delivers your meals?
   d. Housekeeping: Are you able to do housework?
   e. Laundry: Are you able to do your laundry?
   f. Transportation: Do you drive? How do you get to your doctor’s appointments? Do you rely on anyone for transportation?
   g. Medication: How do you take your medication? Do you have a pill box? Does someone set up the medications for you? Are you having difficulty paying for your medications?
   h. Finances: Do you pay your own bills? Does anyone help you with your finances?

4. Mini-Cog:
   a. Instruct the patient to listen carefully and to remember three unrelated words (e.g., red, Broadway, 42), then repeat the three words back to you (to be sure the patient heard them).
   b. Instruct the patient to draw the face of a clock (blank page or with circle already on it).
   c. After the patient puts numbers on the clock face, ask the patient to draw the hands of the clock to read 8:20. No further instructions are to be given. If the clock draw test (CDT) (Fig. 1-1) is not finished after 3 minutes, go to the next step.

FIGURE 1-1. Example of clock draw test. The patient was instructed to have the clock read 3:00.
d. Ask the patient to repeat the three previously presented words.
e. Scoring:
   i. Recall: 0-3 points (1 point for each recalled word after CDT)
   ii. CDT: 0 points for abnl CDT, 2 points for nl CDT (all numbers depicted once, in correct order and position; hands show requested time)
   iii. Add recall and CDT scores to get mini-cog score: 0-5
f. Interpretation: nl >3; abnl <2
5. Get Up and Go Test:
   a. Ask patient to sit in an armless chair.
   b. Instruct patient to stand w/o using hands, walk to a mark 10 feet away, turn, walk back to the chair, and sit again. (If patient is unable to get up w/o the use of hands, then allow the patient to use hands.)
   c. Tell patient that she/he will be timed.
   d. Time get up and go test.
   e. Closely observe body posture while seated, initial stance, stride length, quality of turning, and spatial awareness when seated.
   f. Scoring: time >9 seconds indicates a twofold fall risk.
   g. Check for patient’s comfort. Stand close to the patient to assist if the patient needs support.
6. End-of-life care discussion:
   a. Transition statement: We’ve talked about your current and past medical history. I’d like to ask you about your thoughts regarding your future medical care.
   b. As you look forward in your life, what are some of the things you hope your doctors and family will think about in taking care of you?
   c. What are the things that are most important to you regarding your medical care?
   d. What are the things you worry most about when you think about your medical care in the future?
   e. If appropriate: We’ve just been learning about advanced directives; do you have a living will or durable power of attorney?
   f. If yes: Can you tell me about it?

### DIAGNOSTIC AIDS

1. Rosenbaum Pocket Vision Screener (Fig. 1-2).
2. Grading of cardiac murmurs (Table 1-1).
3. Response of selected murmurs to physiologic intervention (Table 1-2).
4. Folstein Mini-Mental State Examination (Table 1-3).
5. Testing of cranial nerves (Table 1-4).
6. Glasgow Coma Scale (Table 1-5).

<table>
<thead>
<tr>
<th>TABLE 1-1</th>
<th>Grading of Cardiac Murmurs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>Description</td>
</tr>
<tr>
<td>1</td>
<td>Faintest audible; can be heard only w/special effort</td>
</tr>
<tr>
<td>2</td>
<td>Faint but easily audible</td>
</tr>
<tr>
<td>3</td>
<td>Moderately loud</td>
</tr>
<tr>
<td>4</td>
<td>Loud; associated with a thrill</td>
</tr>
<tr>
<td>5</td>
<td>Very loud; associated with a thrill; may be heard w/stethoscope off chest</td>
</tr>
<tr>
<td>6</td>
<td>Maximum loudness; associated with a thrill; heard w/o stethoscope</td>
</tr>
</tbody>
</table>
7. Spinal dermatomes (Fig. 1-3).
8. Key areas determining sensory level (Box 1-1).
9. Key muscles determining motor level (Box 1-2).
10. Grading of muscle strength (Table 1-6).
11. Grading of DTRs (Table 1-7).

**ROSENBAUM POCKET VISION SCREENER**

Card is held in good light 14 inches from eye. Record vision for each eye separately with and without glasses. Presbyopic patients should read thru bifocal segment. Check myopes with glasses only.

**PUPIL GAUGE (mm.)**

*FIGURE 1-2. Rosenbaum chart for testing near vision.*
TABLE 1-2  ■ Response of Selected Murmurs to Physiologic Intervention

<table>
<thead>
<tr>
<th>Cardiac Murmur</th>
<th>Accentuation</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>Valsalva release</td>
<td>Handgrip</td>
</tr>
<tr>
<td></td>
<td>Sudden squatting</td>
<td>Valsalva Standing</td>
</tr>
<tr>
<td></td>
<td>Passive leg raising</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic obstructive cardiomyopathy</td>
<td>Valsalva strain</td>
<td>Handgrip</td>
</tr>
<tr>
<td></td>
<td>Standing</td>
<td>Squatting Leg elevation</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>Sudden squatting</td>
<td>Valsalva Standing</td>
</tr>
<tr>
<td></td>
<td>Isometric handgrip</td>
<td></td>
</tr>
<tr>
<td>Pulmonic stenosis</td>
<td>Valsalva release</td>
<td>Expiration</td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td>Inspiration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Passive leg raising</td>
<td>Expiration</td>
</tr>
<tr>
<td><strong>Diastolic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic insufficiency</td>
<td>Sudden squatting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isometric handgrip</td>
<td></td>
</tr>
<tr>
<td>Mitral stenosis</td>
<td>Exercise</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left lateral position</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isometric handgrip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coughing</td>
<td></td>
</tr>
<tr>
<td>Tricuspid stenosis</td>
<td>Inspiration</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Passive leg raising</td>
<td>Expiration</td>
</tr>
</tbody>
</table>

TABLE 1-3  ■ The Mini-Mental State Examination (MMSE)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orientation: What is the month, day, date, year, season? Where are you? What floor, city, country, state? (Score 1 point for each item correct.)</td>
<td>10</td>
</tr>
<tr>
<td>Registration: State three items (ball, flag, tree). (Score 1 point for each item that the patient registers without having to repeat the words. You may repeat the words until the patient is able to register the words, but do not give the patient credit. You must also tell the patient that he/she should memorize those words and that you will ask him/her to recall those words later.)</td>
<td>3</td>
</tr>
<tr>
<td>Attention: Can you spell the word WORLD forward, then backward? Can you subtract 7 from 100, and keep subtracting 7? (100-93-86-79-72) (Do both items but give credit for the best of the two performances.)</td>
<td>5</td>
</tr>
<tr>
<td>Memory: Can you remember those three words I asked you to memorize? (Do not give clues or multiple choice.)</td>
<td>3</td>
</tr>
<tr>
<td>Language:</td>
<td></td>
</tr>
<tr>
<td>Naming: Can you name (show) a pen and a watch?</td>
<td>2</td>
</tr>
<tr>
<td>Repetition: Can you repeat “No if’s, and’s, or but’s”?</td>
<td>1</td>
</tr>
<tr>
<td>Comprehension: Can you take this piece of paper in your right hand, fold it in half, then put it on the floor? (Score 1 point for each item done correctly.)</td>
<td>3</td>
</tr>
<tr>
<td>Reading: Read and obey “Close your eyes.”</td>
<td>1</td>
</tr>
<tr>
<td>Writing: Can you write a sentence?</td>
<td>1</td>
</tr>
<tr>
<td>Visuospatial: Have patient copy intersecting pentagons.</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
</tr>
</tbody>
</table>

Interpretation: Traditionally, with use of a cutoff score of 23 of 30, the sensitivity and specificity of the MMSE have been reported to be 87% and 82%, respectively, for detection of delirium or dementia in hospitalized patients. However, cognitive performance as measured by the MMSE varies within the population by age and education. To adjust for these variables, it has been proposed that a cutoff score of 19 is appropriate for patients with 0 to 4 years of education and will identify those individuals performing below the level of 75% of their peers; the cutoff score should be 23 for those with 5 to 8 years of education and 27 for those with 9 to 12 years of education. A score below 29 would be abnormal in 75% of individuals with a college education.
### TABLE 1-5 The Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye opening</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously</td>
<td>4</td>
</tr>
<tr>
<td>To verbal command</td>
<td>3</td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Verbal response</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oriented-converses</td>
<td>5</td>
</tr>
<tr>
<td>Disoriented-converses</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Motor response</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obey verbal commands</td>
<td>6</td>
</tr>
<tr>
<td>Localizes to painful stimuli</td>
<td>5</td>
</tr>
<tr>
<td>Flexion withdrawal</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion</td>
<td>3</td>
</tr>
<tr>
<td>Extension</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>
**Box 1-1 • Key Areas Determining Sensory Level**

<table>
<thead>
<tr>
<th>C2</th>
<th>Occipital protuberance</th>
<th>T6</th>
<th>Sixth intercostal space, xiphisternum</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>Supraclavicular fossa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>Top of the acromioclavicular joint</td>
<td>T7-9</td>
<td>Intercostal spaces</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T10</td>
<td>Umbilicus</td>
</tr>
<tr>
<td>C5</td>
<td>Lateral side of the antecubital fossa</td>
<td>T11</td>
<td>Intercostal space</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T12</td>
<td>Inguinal ligament</td>
</tr>
<tr>
<td>C6</td>
<td>Thumb</td>
<td>L1</td>
<td>Upper anterior thigh</td>
</tr>
<tr>
<td>C7</td>
<td>Middle finger</td>
<td>L2</td>
<td>Midanterior thigh</td>
</tr>
<tr>
<td>C8</td>
<td>Little finger</td>
<td>L3</td>
<td>Medial femoral condyle</td>
</tr>
<tr>
<td>T1</td>
<td>Medial side of the antecubital fossa</td>
<td>L4</td>
<td>Medial malleolus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L5</td>
<td>Dorsum of the foot at the third metatarsophalangeal joint</td>
</tr>
<tr>
<td>T2</td>
<td>Apex of the axilla</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Third intercostal space</td>
<td>S1</td>
<td>Lateral heel</td>
</tr>
<tr>
<td>T4</td>
<td>Fourth intercostal space, nipple line</td>
<td>S2</td>
<td>Popliteal fossa in the midline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S3</td>
<td>Ischial tuberosity</td>
</tr>
<tr>
<td>T5</td>
<td>Fifth intercostal space</td>
<td>S4-5</td>
<td>Perianal area</td>
</tr>
</tbody>
</table>

**FIGURE 1-3.** Spinal dermatomes.
**Box 1-2 - Key Muscles Determining Motor Level**

<table>
<thead>
<tr>
<th>C1-4</th>
<th>Diaphragm</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Elbow flexors (biceps)</td>
</tr>
<tr>
<td>C6</td>
<td>Wrist extensors</td>
</tr>
<tr>
<td>C7</td>
<td>Elbow extensors (triceps)</td>
</tr>
<tr>
<td>C8</td>
<td>Finger flexors, distal phalanx</td>
</tr>
<tr>
<td>T1</td>
<td>Hand intrinsics (interossei)</td>
</tr>
<tr>
<td>T2-L1</td>
<td>Use sensory level and Beevor’s sign</td>
</tr>
<tr>
<td>L2</td>
<td>Hip flexors (iliopsoas)</td>
</tr>
<tr>
<td>L3</td>
<td>Knee extensors (quadriceps)</td>
</tr>
<tr>
<td>L4</td>
<td>Ankle dorsiflexors (tibialis anterior)</td>
</tr>
<tr>
<td>L5</td>
<td>Long toe extensors (extensor hallucis longus)</td>
</tr>
<tr>
<td>S1</td>
<td>Ankle plantar flexors (gastrocnemius)</td>
</tr>
<tr>
<td>S2-5</td>
<td>Use sensory level and sphincter ani</td>
</tr>
</tbody>
</table>

**TABLE 1-6 - Grading of Muscle Strength**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent muscle contraction</td>
</tr>
<tr>
<td>1</td>
<td>Minimal contraction</td>
</tr>
<tr>
<td>2</td>
<td>Active movement with gravity eliminated</td>
</tr>
<tr>
<td>3</td>
<td>Active movement against gravity only</td>
</tr>
<tr>
<td>4</td>
<td>Active movement against gravity and some resistance</td>
</tr>
<tr>
<td>5</td>
<td>Normal muscle strength</td>
</tr>
</tbody>
</table>

**TABLE 1-7 - Grading of Deep Tendon Reflexes**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absent</td>
</tr>
<tr>
<td>+</td>
<td>Hypoactive</td>
</tr>
<tr>
<td>++</td>
<td>Normal</td>
</tr>
<tr>
<td>+++</td>
<td>Brisker than average</td>
</tr>
<tr>
<td>++++</td>
<td>Hyperactive, often indicative of disease</td>
</tr>
</tbody>
</table>

**B. Charting**

**1 ADMISSION ORDERS**

A. Admit to: indicate ward where patient is being admitted and attending physician [e.g., coronary care unit (CCU), Dr. Smith’s service].

B. Because: indicate admitting dx (e.g., chest pain).

C. Condition: patient’s general condition (stable, fair, poor, critical).

   Code status: DNR, full code, CMO.

   Consults:

D. Diet: specify whether regular, clear liquids, NAS, ADA, low cholesterol, other.

   DVT prophylaxis:

   A. Allergies: indicate medications (including OTC medications) and specific food products to which the patient has experienced an allergic reaction.

   Activity: specify bed rest, ad lib, bathroom privileges.

   V. Vital signs: specify frequency (e.g., qid, q4h); also indicate any special nursing orders (e.g., VS and neurologic signs qh x 24h, then q4h if stable).

   I. IV fluids: specify any IV solutions and rate of infusion.

   D. Diagnostic tests: laboratory tests, x-rays, ECG, special tests.

   Drugs: indicate medication, dose, frequency, special restrictions (e.g., atenolol 50 mg PO qd; if HR <50 bpm, hold atenolol and notify house officer).
2. **VS:**
   a. **BP:**
   b. **Pulse:**
   c. **Respirations:**
   d. **Temperature:**

2. **General description:** The patient is a (age, sex) who looks her stated age, is pleasant, appears to be well nourished, and seems in a good state of health.

3. **Skin:** The skin is warm and dry; turgor is adequate; color is normal. There is no icterus, purpura, rash, or unusual pigmentation noted. Hair is normal in appearance, distribution, and texture.

4. **Lymph nodes:** There is no cervical, supraclavicular, axillary, epitrochlear, or inguinal adenopathy.

5. **HEENT:**
   a. **Head:** Normocephalic and atraumatic; no lesions noted.
   b. **Eyes:** Cornea is without lesion, conjunctiva is clear, sclera is white. Pupils are equal, measuring approximately 3 mm in diameter, round, and reactive to light and accommodation. Extraocular movements are within normal limits without any nystagmus or strabismus. Fundi appear benign. Disks are well delineated. There are no hemorrhages or exudates. Visual acuity is 20/20 bilaterally, and visual fields are within normal limits.
   c. **Ears:** Ears are normal in appearance. Auditory canal appears clean and without lesions. The tympanic membranes are intact. Hearing is adequate.
   d. **Nose:** Septum appears to be within normal limits and without deviation. Nasal mucosa appears pink and without any abnormal discharge. No nasal polyps or other lesions are noted. Frontal and maxillary sinuses are nontender.
   e. **Mouth and throat:** Lips are without cyanosis or pallor. Buccal mucosa is normal in appearance. Teeth appear to be in good condition. Tongue shows no lesions or tremor. Pharyngeal mucosa is pink and does not reveal any lesions, exudates, erythema, or evidence of inflammation. Gag reflex is intact.

6. **Neck:** Neck is supple. Full range of motion is present. There is no evidence of tracheal deviation, JVD, or lymphadenopathy. Carotid pulses are 2+, equal bilaterally, and without bruits. Carotid upstroke is within normal limits. Thyroid gland is normal in size; its palpation does not reveal any nodules or masses.

7. **Back:** Spinal curvature is normal; there is no scoliosis, kyphosis, or tenderness present. Full range of motion is present.

8. **Chest:** Thorax is symmetric. Full expansion is noted bilaterally. Anterior-posterior diameter is within normal limits.

9. **Lungs:** Fremitus is equal bilaterally. Lung fields are resonant throughout. Breath sounds and voice sounds are normal. There are no rales or rhonchi.

10. **Heart:** Palpation reveals no heaves or thrills. The PMI is medial to the midclavicular line, fourth intercostal space. Auscultation reveals S₁, S₂ of normal intensity. There are no S₃, S₄, rubs, clicks, or other abnormal heart sounds. Heart rate is approximately 70 bpm and rhythm is regular.

11. **Breasts (female patient):** Breasts are symmetric and have a normal contour. Skin is of normal color and appearance; there is no edema, ulceration, or erythema. Nipples are of normal size and shape; there is no nipple retraction, ulceration, or discharge. Palpation does not reveal any tenderness or masses.

12. **Abdomen:** Abdomen is of normal size and contour. There are no capillary dilatations, skin lesions, or surgical scars noted. Auscultation
reveals normoactive bowel sounds and no abdominal bruits. Palpation reveals no abdominal tenderness, guarding, or masses. The liver edge is felt approximately 1 inch below the right costal margin; it is firm, sharp, and smooth. The liver percusses to approximately 8 to 10 cm in total span. The spleen is not palpable.

13. Rectal examination: Rectal examination reveals no external anal lesions. Sphincter tone is normal. There are no internal or external hemorrhoids. Rectal mucosa appears normal, and there are no nodules or masses present. Stool is brown and negative for occult blood. Male patient: Prostate is normal in size, no nodules.

14. Genitalia: Inspection reveals normal distribution of pubic hair. Female patient: Clitoris and labia are without lesions. Internal examination with speculum reveals normal vaginal wall. The cervical os is well visualized. No lesions or discharges are noted. A specimen was obtained for cervical cytology. Bimanual examination reveals no cervical tenderness or masses. Uterus and ovaries are nontender and of normal size.

15. Inguinal area: There is no lymphadenopathy noted. Femoral tenderness are 2+ and equal bilaterally. Auscultation reveals no femoral bruits.

16. Extremities: There is no clubbing, cyanosis, or edema. Brachial, radial, popliteal, dorsalis pedis, and posterior tibial pulses are 2+ and equal bilaterally. Musculoskeletal examination reveals no joint deformities and full range of motion. There is no bone, joint, or muscle tenderness noted.

17. Neurologic: Patient is alert and oriented to time, person, and place. Cranial nerves II to XII are within normal limits. Speech, memory, and expression are within normal limits. Muscle strength is 5/5 in both upper and lower extremities. There is no muscle atrophy or involuntary movement noted. Testing of cerebellar function reveals normal gait, negative Romberg test result, and good coordination in finger-to-nose, heel-to-shin, and alternate motion testing. Sensory is intact to light touch, pain, and vibratory stimuli. There are no focal motor or sensory deficits present. Deep tendon reflexes are 2+ and equal bilaterally.

**4 PROGRESS (SOAP) NOTE**

S. Subjective: observations, patient complaints.

O. Objective: description of physical findings and recording of laboratory, x-ray, or ECG data.

A. Assessment: analysis of data and tentative dx.

P. Plan: diagnostic studies and therapeutic regimen.

**5 CONSULT NOTE**

- Date/time
- Reason for consult
- HPI
- Current medications
- Physical exam
- Impression
- Recommendations

**6 PREOPERATIVE NOTE**

- Date and time
- Preoperative dx
- Surgeon of record
- Planned procedure
- Consent
- Labs
- CXR
- ECG
- Blood
- Important imaging studies summarized (CT, angiography, MRI)
- Orders
7 OPERATIVE NOTE

- Date and time
- Preoperative dx (presumed dx)
- Postoperative dx (actual dx)
- Primary surgeon
- Assistants
- Indications
- Operation performed
- CPT code (if known)
- Wound class (if known)
- Procedure in detail (include abx, time-out procedure, consent documented in chart, amount of local anesthetic, DVT prophylaxis, sponge count)
- Findings (include important aspects of the operation, e.g., tumor margins, frozen pathology, type of anastomosis and involved vessels, intraoperative imaging results [such as cholangiography, angiography, fluoroscopy], perforated or nonperforated appendix)
- Fluids (type and amount; include blood products)
- Estimated blood loss
- Urine output
- Drains or tubes (type and site)
- Specimens and cultures
- Complications
- Disposition (patient status at end of case)
- Presence of attending surgeon (e.g., the attending was present and participated in all aspects of the case)

8 PROCEDURE NOTE

- Date and time
- Procedure
- Consent form
- Indications
- Physicians
- Description
- Findings
- Complications
- Disposition

9 DISCHARGE SUMMARY

The discharge summary should contain only essential information about the investigation and treatment of the patient’s illness. It should briefly describe the following:
- Why the patient entered the hospital: a brief statement of the CC, admission dx, and HPI.
- The pertinent laboratory, x-ray, and physical findings; negative findings may be as pertinent as positive findings.
- The medical or surgical treatment, including the patient’s response, any complications, and consultations; a rationale for what was or was not done.
- The patient’s condition when discharged (ambulation, self-care, ability to work).
- Instructions given on continuing care, such as medication by name and specific dosage, diet, type and amount of physical activity, other therapeutic measures, referrals, and appointments.
- The principal dx and additional or secondary diagnoses.

10 PRONOUNCING DEATH WHILE ON CALL

The legal criteria of death fall within state jurisdiction. One should become familiar with the accepted definition of death in one’s own state. When called to pronounce a patient dead, the following steps should be followed:
1. Identify the patient (examine hospital ID tag on the patient’s wrist).
2. Examine patient for:
   a. Response to verbal or tactile stimuli (none)
   b. Spontaneous respiration (none)
   c. Heart sounds and pulses (absent)
   d. Pupillary response (pupils fixed and dilated)
3. Document the time the patient was pronounced dead (legal time of death).
4. Notify attending physician (if not already done by the nursing staff) and inquire if family requests autopsy. Notify the organ bank for possible organ donation, if this is consistent with your hospital’s policy.
5. Document findings in patient’s chart (e.g., “Called by charge nurse to pronounce Mr. John Smith dead. Patient examined, unresponsive to verbal or tactile stimuli, no spontaneous respiration noted, heart sounds not audible, pulses absent, pupils fixed and dilated. Patient pronounced dead at 11:10 PM. Attending notified. Next of kin to be contacted by attending.”) The attending will often not be available, and you will be asked to notify the next of kin.
   a. Familiarize yourself with the patient’s medical hx and mode of death.
   b. Identify yourself to the family in a humble and caring manner and inform them that their next of kin has expired. Inform them of the time that the patient was pronounced dead, and always try to comfort them that their relative died peacefully.
   c. If it is not clear from the patient’s records, inquire if the family requests an autopsy.
   d. Ask the next of kin if the family will be coming to the hospital to view the body before it is transported to the hospital morgue. Notify the charge nurse of their decision.

**DISCHARGE AGAINST MEDICAL ADVICE (AMA)**

1. Discharge AMA, in which a patient chooses to leave the hospital before the treating physician recommends discharge, occurs in nearly 2% of medical admissions.
2. Risk factors are h/o substance or EtOH abuse, lack of insurance or Medicaid, younger age, and male sex.
3. Strategies for preventing AMA discharges include proactively addressing substance abuse issues and recognizing and treating psychological factors. Motivational interviewing, which relies on the principle of patient-centered interviewing and use of nonjudgmental empathetic questioning, is an effective modality in lowering the risk of discharge AMA.
4. If prevention of discharge AMA is not successful, informed consent is a crucial element in managing an AMA discharge. An informed decision means that the decision has been made by the patient in consultation with the physician without being coerced and with a full understanding of the risks, benefits, and alternatives of the decision.
5. The evaluation of the patient being discharged AMA should include the following:
   a. Does the patient understand and appreciate the admission dx, prognosis, and risks and benefits of leaving the hospital? It is important to document that the patient understands the information, terminology, and language (has adequate health literacy).
   b. Is the patient aware of alternative treatments outside of the hospital and associated risks and benefits?
   c. Is the patient able to make and communicate his/her choice?
   d. Can the patient articulate a reason for the choice that is consistent with his/her choice?
6. If a patient is deemed to be without decision-making capacity and has no surrogate, consultation with a psychiatrist may be helpful to keep the patient in the hospital against his/her will.
7. Managing an AMA discharge also includes ensuring that the discharge is as safe as possible under the circumstances and helping the patient follow up after discharge.
C. Evaluating the Labs

This section covers more than 200 laboratory tests. Each test is approached with the following format:

1. Laboratory test.
2. Normal range in adult patients.
3. Common abnormalities (e.g., positive test result, increased or decreased value).
4. Causes of abnormal result.

The normal ranges may differ slightly, depending on the laboratory. The reader should be aware of the “normal range” of the particular laboratory performing the test. Every attempt has been made to present current laboratory test data with emphasis on practical considerations. It is important to remember that lab tests do not make diagnoses, physicians do. As such, any lab results should be integrated with the complete clinical picture and radiographic studies (if needed) to make a dx.

**ACE LEVEL; see ANGIOTENSIN-CONVERTING ENZYME**

**ACETONE (Serum or Plasma)**

**Normal:** Negative.

**Elevated in:** DKA, starvation, isopropanol ingestion.

**ACETYLCHOLINE RECEPTOR (AChR) ANTIBODY**

**Normal:** <0.03 nmol/L.

**Elevated in:** myasthenia gravis. Changes in AChR concentration correlate w/ the clinical severity of myasthenia gravis after Rx and during Rx w/ prednisone and immunosuppressants. False-positive AChR Ab results may be found in pts w/Eaton-Lambert syndrome.

**ACID PHOSPHATASE (Serum)**

**Normal range:** enzymatic, prostatic, 0-5.5 U/L; enzymatic, total, 2-12 U/L.

**Elevated in:** carcinoma of prostate, other neoplasms (breast, bone), Paget’s disease of bone, hemolysis, MM, osteogenesis imperfecta, malignant invasion of bone, Gaucher’s disease, myeloproliferative disorders, prostatic palpation or surgery, hyperparathyroidism, liver disease, chronic renal failure, ITP.

**ACTIVATED CLOTTING TIME (ACT)**

**Normal:** This test is used to determine the dose of protamine sulfate to reverse the effect of heparin as an anticoagulant during angioplasty, cardiac surgery, and hemodialysis. The accepted goal during cardiopulmonary bypass surgery is usually 400 to 500 seconds.

**ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT); see PARTIAL THROMBOPLASTIN TIME**

**ADRENOCORTICOTROPIC HORMONE (ACTH)**

**Normal:** 9-52 pg/mL.

**Elevated in:** Addison’s disease, ectopic ACTH-producing tumors, congenital adrenal hyperplasia, Nelson’s syndrome, pituitary-dependent Cushing’s disease.

**Decreased in:** secondary adrenocortical insufficiency, hypopituitarism, adrenal adenoma or adrenal carcinoma.
ALANINE AMINOTRANSFERASE (ALT, SGPT)

Normal range: 8-35 U/L (female); 10-40 U/L (male).
Elevated in: liver disease (e.g., hepatitis, cirrhosis, Reye’s syndrome), EtOH abuse, drugs (e.g., acetaminophen, statins, NSAIDs, abx, anabolic steroids, narcotics, heparin, labetalol, amiodarone, chlorpromazine, phenytoin), hepatic congestion, infectious mononucleosis, liver mets, MI, myocardiitis, severe muscle trauma, dermatomyositis or polymyositis, muscular dystrophy, malignant neoplasms, renal and pulmonary infarction, convulsions, eclampsia, dehydration (relative increase), Chinese herbs.
Decreased in: azotemia, advanced malnutrition, chronic renal dialysis, chronic alcoholic liver disease, metronidazole.

ALBUMIN (Serum)

Normal range: 4-6 g/dL.
Elevated in: dehydration (relative ↑), IV alb infusion.
Decreased in: liver disease, nephrotic syndrome, poor nutritional status, rapid IV hydration, protein-losing enteropathies (IBD), severe burns, neoplasia, chronic inflammatory diseases, pregnancy, prolonged immobilization, lymphomas, hypervitaminosis A, chronic GN.

ALDOLASE (Serum)

Normal range: 0-6 U/L.
Elevated in: rhabdo, dermatomyositis or polymyositis, trichinosis, acute hepatitis and other liver diseases, muscular dystrophy, MI, prostatic carcinoma, hemorrhagic pancreatitis, gangrene, delirium tremens, burns.
Decreased in: loss of muscle mass, late stages of muscular dystrophy.

ALDOSTERONE (Plasma)

Normal: 3-16 ng/dL (adult supine); 7-30 ng/dL (adult upright); 200-800 ng/dL (adrenal vein).
Elevated in: aldosterone-secreting adenoma, bilateral adrenal hyperplasia, secondary aldosteronism (diuretics, CHF, laxatives, nephritic syndrome, cirrhosis w/ascites, Bartter’s syndrome, pregnancy, starvation).

ALKALINE PHOSPHATASE (Serum)

Normal range: 30-120 U/L.
Elevated in: biliary obstruction, cirrhosis (particularly PBC), liver disease (hepatitis, infiltrative liver diseases, fatty metamorphosis), Paget’s disease of bone, osteitis deformans, rickets, osteomalacia, hypervitaminosis D, hyperparathyroidism, hyperthyroidism, UC, bowel perforation, bone mets, healing fxs, bone neoplasms, acromegaly, infectious mononucleosis, CMV infections, sepsis, pulmonary infarction, hypernephroma, leukemia, myelofibrosis, MM, drugs (estrogens, alb, erythromycin and other abx, cholestasis-producing drugs [phenothiazines]), pregnancy, puberty, postmenopausal females.
Decreased in: hypothyroidism, pernicious anemia, hypophosphatemia, hypervitaminosis D, malnutrition.

ALPHA1-FETOPROTEIN (Serum)

Normal range: 0-20 ng/mL.
Elevated in: Hepatocellular carcinoma (usually values >1000 ng/mL), germinal neoplasms (testis, ovary, mediastinum, retroperitoneum), liver disease (alcoholic cirrhosis, acute hepatitis, chronic active hepatitis), fetal anencephaly, spina bifida, basal cell carcinoma, breast carcinoma, pancreatic carcinoma, gastric carcinoma, retinoblastoma, esophageal atresia.
ALANINE AMINOTRANSFERASE

ALUMINUM (Serum)

Normal range: 0-6 ng/mL.
Elevated in: chronic renal failure on dialysis, parenteral nutrition, industrial exposure.

AMA; see MITOCHONDRIAL ANTIBODY

AMMONIA (Serum)

Normal range: 15–45 µg/dL (adults); 29–70 µg/dL (children).
Elevated in: hepatic failure, hepatic encephalopathy, Reye’s syndrome, portacaval shunt, drugs (diuretics, polymyxin B, methicillin).
Decreased in: drugs (neomycin, lactulose), renal failure.

AMYLASE (Serum)

Normal range: 0-130 U/L.
Elevated in: acute pancreatitis, macroamylasemia, salivary gland inflammation, mumps; pancreatic neoplasm, abscess, pseudocyst, ascites; perforated peptic ulcer; intestinal obstruction, intestinal infarction; acute cholecystitis, appendicitis, ruptured ectopic pregnancy, peritonitis, burns, DKA, renal insufficiency; drugs (morphine); carcinomatosis of lung, esophagus, ovary; acute ethanol ingestion; prostate tumors; post-ERCP; bulimia, anorexia nervosa.
Decreased in: advanced chronic pancreatitis, hepatic necrosis, cystic fibrosis.

AMYLASE, URINE; see URINE AMYLASE

ANA; see ANTINUCLEAR ANTIBODY

ANCA; see ANTINEUTROPHIL CYTOPLASMIC ANTIBODY

ANDROSTEDIONE (Serum)

Normal: 75–205 ng/dL (male); 85-275 ng/dL (female).
Elevated in: congenital adrenal hyperplasia, polycystic ovary syndrome, ectopic ACTH-producing tumor, Cushing’s syndrome, hirsutism, hyperplasia of ovarian stroma, ovarian neoplasm.
Decreased in: ovarian failure, adrenal failure, sickle cell anemia.

ANGIOTENSIN II

Normal: 10-60 pg/mL.
Elevated in: HTN, CHF, cirrhosis, renin-secreting renal tumor, volume depletion.
Decreased in: ACEIs, ARB drugs, primary aldosteronism, Cushing’s syndrome.

ANGIOTENSIN-CONVERTING ENZYME (ACE Level)

Normal range: <40 nmol/mL/min.
Elevated in: sarcoidosis, PBC, alcoholic liver disease, hyperthyroidism, hyperparathyroidism, DM, amyloidosis, MM, lung disease (asbestosis, silicosis, berylliosis, allergic alveolitis, coccidioidomycosis), Gaucher’s disease, leprosy.
Decreased in: ACEI Rx.

ANION GAP

Normal range: 9-14 mEq/L.
Elevated in: lactic acidosis, ketoacidosis (DKA, alcoholic starvation), uremia (chronic renal failure), ingestion of toxins (paraldehyde, methanol, salicylates, ethylene glycol), hyperosmolar nonketotic coma, abx (carbenicillin).
Decreased in: hypoalbuminemia, severe hypermagnesemia, IgG myeloma, lithium toxicity, laboratory error (falsely decreased sodium or overestimation of HCO₃ or chloride), hypercalcemia of parathyroid origin, abx (e.g., polymyxin).

**ANTICARDIOLIPIN ANTIBODY (ACA)**

**Normal range:** negative. Test includes detection of IgG, IgM, and IgA Ab to phospholipid, cardiolipin.

**Present in:** antiphospholipid Ab syndrome, chronic HCV infection.

**ANTICOAGULANT; see** CIRCULATING ANTICOAGULANT

**ANTIDIURETIC HORMONE (ADH)**

**Normal:** 295-300 mOsm/kg; 4-12 pg/mL.

**Elevated in:** SIADH, antipsychotic meds, ectopic ADH from systemic neoplasm, GBS, CNS infections, brain tumors, nephrogenic diabetes insipidus.

**Decreased in:** central diabetes insipidus, nephritic syndrome, psychogenic polydipsia, demeclocycline, lithium, phenytoin, EtOH.

**ANTI-DNA**

**Normal range:** absent.

**Present in:** SLE, chronic active hepatitis, infectious mononucleosis, biliary cirrhosis.

**ANTI-DS DNA**

**Normal:** <25 U.

**Elevated in:** SLE.

**ANTIGLOBULIN TEST, DIRECT; see** COOMBS, DIRECT

**ANTI–GLOMERULAR BASEMENT ANTIBODY; see** GLOMERULAR BASEMENT MEMBRANE ANTIBODY

**ANTI-HCV; see** HEPATITIS C ANTIBODY

**ANTIHISTONE**

**Normal:** <1 U.

**Elevated in:** drug-induced lupus erythematosus.

**ANTIMITOCHONDRIAL ANTIBODY (AMA)**

**Normal range:** <1:20 titer.

**Elevated in:** PBC (85%-95%), chronic active hepatitis (25%-30%), cryptogenic cirrhosis (25%-30%).

**ANTINEUROPHIL CYTOPLASMIC ANTIBODY (ANCA)**

**Positive test result:**
- Cytoplastic pattern (cANCA): positive in Wegener’s granulomatosis.
- Perinuclear pattern (pANCA): positive in IBD, PBC, PSC, autoimmune chronic active hepatitis, crescentic GN.

**ANTINUCLEAR ANTIBODY (ANA)**

**Normal range result:** <1:20 titer.

**Positive test:** SLE (more significant if titer >1:160), drugs (phenytoin, ethosuximide, primidone, methyldopa, hydralazine, carbamazepine, PCN, procainamide, chlorpromazine, griseofulvin, thiazides), chronic active hepatitis, age >60 years (particularly age >80 years), RA, scleroderma, MCTD, necrotizing vasculitis, Sjögren’s syndrome.

Figure 1-5 describes diagnostic tests and diagnoses to consider from ANA pattern.
Homogeneous pattern (diffuse)  
Associated with  
SLE  
MCTD

Outline pattern (peripheral)  
Associated with  
SLE

Speckled pattern  
Associated with  
SLE  
Scleroderma  
Rheumatoid arthritis  
MCTD

Nucleolar pattern  
Associated with  
Scleroderma  
Polymyositis

**FIGURE 1-5.** Patterns of immunofluorescent staining of antinuclear antibodies and the diseases with which they are associated.

**ANTIPHOSPHOLIPID ANTIBODY; see**  
**LUPUS ANTICOAGULANT**

**ANTI-RNP ANTIBODY; see**  
**EXTRACTABLE NUCLEAR ANTIGEN**

**ANTI–SCL-70**  
Normal: absent.  
Elevated in: scleroderma.

**ANTI–SM (ANTI-SMITH) ANTIBODY; see**  
**EXTRACTABLE NUCLEAR ANTIGEN**

**ANTI–SMOOTH MUSCLE ANTIBODY; see**  
**SMOOTH MUSCLE ANTIBODY**

**ANTISTREPTOLYSIN O TITER (Streptozyme, ASO, ASLO Titer)**  
Normal range for adults: <160 Todd units.  
Elevated in: streptococcal upper airway infection, acute rheumatic fever, AGN, increased levels of β-lipoprotein (false-positive ASLO test result).
Note: A fourfold increase in titer between acute and convalescent specimens is diagnostic of streptococcal upper airway infection regardless of the initial titer.

ANTITHROMBIN III

Normal range: 81%-120% of nl activity; 17-30 mg/dL.
Decreased in: hereditary deficiency of antithrombin III, DIC, PE, cirrhosis, thrombolytic Rx, chronic liver failure, postsurgery, third trimester of pregnancy, oral contraceptives, nephrotic syndrome, IV heparin >3 days, sepsis, acute leukemia, carcinoma, thrombophlebitis.
Elevated in: warfarin Rx, post-MI.

APOLIPOPROTEIN A-1 (Apo A-1)

Normal: recommended >120 mg/dL.
Elevated in: familial hyperalphalipoproteinemia, statins, niacin, estrogens, weight loss, familial cholesteryl ester transfer protein (CETP) deficiency.
Decreased in: familial hypoalphalipoproteinemia, Tangier disease, diuretics, androgens, cigarette smoking, hepatocellular disorders, chronic renal failure, nephritic syndrome, coronary heart disease, cholestasis.

APOLIPOPROTEIN B (Apo B)

Normal: desirable <100 mg/dL; high risk >120 mg/dL.
Elevated in: high-saturated fat diet, high-cholesterol diet, hyperapobetalipoproteinemia, familial combined hyperlipidemia, anabolic steroids, diuretics, β-blockers, corticosteroids, progestins, diabetes, hypothyroidism, chronic renal failure, liver disease, Cushing’s syndrome, coronary heart disease.
Decreased in: statins, niacin, low-cholesterol diet, malnutrition, abetalipoproteinemia, hypobetalipoproteinemia, hyperthyroidism.

ARTERIAL BLOOD GASES (ABGs)

Normal range:
- PO₂: 75-100 mm Hg
- PCO₂: 35-45 mm Hg
- HCO₃⁻: 24-28 mEq/L
- pH: 7.35-7.45

Abnormal values: Refer to individual acid-base disturbances in Section 3.

ASLO TITER; see ANTISTREPTOLYSIN O TITER

ASPARTATE AMINOTRANSFERASE (AST, SGOT)

Normal range: 0-35 U/L.
Elevated in: liver disease (hepatitis, hemochromatosis, cirrhosis, Reye’s syndrome, Wilson’s disease), EtOH abuse, drugs (acetaminophen, statins, NSAIDs, ACEIs, heparin, labetalol, phenytoin, amiodarone, chlorpromazine), hepatic congestion, infectious mononucleosis, MI, myocarditis, severe muscle trauma, dermatomyositis and polymyositis, muscular dystrophy, malignant neoplasia, renal and pulmonary infarction, convulsions, eclampsia.
Decreased in: uremia, vitamin B₆ deficiency.

BASOPHIL COUNT

Normal range: 0.4%-1% of total WBCs; 40-100/mm³.
Decreased in: stress, hypersensitivity reaction, steroids, pregnancy, hyperthyroidism.

BICARBONATE

Normal: 21-28 mEq/L (arterial); 22-29 mEq/L (venous).
Elevated in: metabolic alkalosis, compensated respiratory acidosis, diuretics, corticosteroids, laxative abuse.
Decreased in: metabolic acidosis, compensated respiratory alkalosis; acetazolamide, cyclosporine, cholestyramine, methanol or ethylene glycol poisoning.

**BLOOD VOLUME, TOTAL**

**Normal:** 60-80 mL/kg.

**Elevated in:** anemia, hemorrhage, vomiting, diarrhea, dehydration, burns, starvation.

**Decreased in:** P vera, pulmonary disease, CHF, renal insufficiency, pregnancy, acidosis, thyrotoxicosis.

**BLOOD VOLUME, TOTAL**

Normal: The test determines the radioactivity of $^{14}$CO$_2$ in breath samples at 2 and 4 hours.

- 2 hours after dose: $0.11 \pm 0.14$
- 4 hours after dose: $0.52 \pm 0.09$

**Elevated in:** GI bacterial overgrowth, cimetidine.

**BILIRUBIN, DIRECT (Conjugated Bilirubin)**

**Normal range:** 0-0.2 mg/dL.

**Elevated in:** hepatocellular disease, biliary obstruction, drug-induced cholestasis, hereditary disorders (Dubin-Johnson syndrome, Rotor’s syndrome), advanced neoplastic states.

**BILIRUBIN, INDIRECT (Unconjugated Bilirubin)**

**Normal range:** 0-1.0 mg/dL.

**Elevated in:** hemolysis, liver disease (hepatitis, cirrhosis, neoplasm), hepatic congestion caused by CHF, hereditary disorders (Gilbert’s disease, Crigler-Najjar syndrome).

**BILIRUBIN, TOTAL**

**Normal range:** 0-1.0 mg/dL.

**Elevated in:** liver disease (hepatitis, cirrhosis, cholangitis, neoplasm, biliary obstruction, infectious mononucleosis), hereditary disorders (Gilbert’s disease, Dubin-Johnson syndrome), drugs (steroids, diphenylhydantoin, phenothiazines, PCN, erythromycin, clindamycin, captopril, amphotericin B, sulfonamides, azathioprine, isoniazid, 5-aminosalicylic acid, allopurinol, methyldopa, indomethacin, halothane, oral contraceptives, procainamide, tolbutamide, labetalol), hemolysis, pulmonary embolism or infarct, hepatic congestion resulting from CHF.

**BILIRUBIN, URINE; see URINE BILE**

**BLEEDING TIME (Modified Ivy Method)**

**Normal range:** 2-9.5 minutes.

**Elevated in:** thrombocytopenia, capillary wall abnormalities, platelet abnormalities (Bernard-Soulier disease, Glanzmann’s disease), drugs (ASA, warfarin, anti-inflammatory medications, streptokinase, urokinase, dextran, $\beta$-lactam abx, moxalactam), DIC, cirrhosis, uremia, myeloproliferative disorders, vWD.

**Comments:** The bleeding time test as a method to evaluate suspected hemostatic incompetence has been replaced in many laboratories by platelet function analysis (PFA-100 assay). The bleeding time test’s ability to predict excessive bleeding in clinical situations, such as surgery or invasive diagnostic procedures, is poor. It may play a limited residual role in the evaluation of suspected hereditary disorders of hemostasis.
BNP; see B-TYPE NATRIURETIC PEPTIDE

**BRCA-1, BRCA-2**

This test involves the detection of carriers of mutations in the genes characterized by predisposition to breast and ovarian cancers. These mutations occur in about 1 in 300 to 500 women in the general population and in about 2% of Ashkenazi Jewish women. Women found to carry the mutation should undergo earlier and more intensive surveillance for breast cancer. Pre-test counseling should be provided before genetic testing. The U.S. Preventive Services Task Force recommends screening in the following:

1. Non-Ashkenazi women:
   a. Two first-degree relatives w/breast or ovarian cancer (including one diagnosed ≤50 years of age).
   b. Three or more first- or second-degree relatives w/breast cancer.
   c. Both breast cancer and ovarian cancer among first- and second-degree relatives.
   d. A first-degree relative w/bilateral breast cancer.
   e. Two or more first- or second-degree relatives w/ovarian cancer.
   f. A first- or second-degree relative w/both breast and ovarian cancer
   g. A male relative w/breast cancer.

2. Ashkenazi women:
   a. Any first-degree relative w/breast or ovarian cancer.
   b. Two second-degree relatives on the same side of the family w/breast or ovarian cancer.

**BREATH HYDROGEN TEST**

**Normal**: This test is for bacterial overgrowth \( H_2 \) excretion; fasting:
- 4.6 ± 5.1; after lactulose: early increase <12. Lactulose usually results in a colonic response >30 minutes after ingestion.

**Elevated in**: A high fasting breath \( H_2 \) level and an increase of at least 12 ppm within 30 minutes after lactulose challenge are indicative of bacterial overgrowth in the small intestine. The increase must precede the colonic response.

**Fast positives in**: accelerated gastric emptying, laxative use.

**Fast negatives in**: use of abx and pts who are non-hydrogen producers.

**B-TYPE NATRIURETIC PEPTIDE (BNP)**

**Normal range**: up to 100 µg/L. Natriuretic peptides are secreted to regulate fluid volume, BP, and electrolyte balance. They have activity in the central and peripheral nervous system. In humans, the main source of circulatory BNP is the heart ventricles.

**Elevated in**: heart failure. This test is useful in the emergency department setting to differentiate heart failure pts from those w/COPD presenting w/dyspnea. Levels are also increased in asymptomatic left ventricular dysfunction, arterial and pulmonary HTN, cardiac hypertrophy, valvular heart disease, arrhythmia, and ACS.

**BUN; see UREA NITROGEN**

**C3; see COMPLEMENT C3**

**C4; see COMPLEMENT C4**

**CALCITONIN (Serum)**

**Normal range**: <100 pg/mL.

**Elevated in**: medullary carcinoma of the thyroid (particularly if level >1500 pg/mL), carcinoma of the breast, apudomas, carcinoids, renal failure, thyroiditis.

**CALCIUM (Serum)**

**Normal range**: 8.8-10.3 mg/dL.

**Abnormal values**: Refer to Section 3.
CALCIUM, URINE; see URINE CALCIUM

CAPTOPRIL STIMULATION TEST
Normal: The test is performed by giving 25 mg captopril PO after an overnight fast. The patient should be seated during the test. After captopril, aldosterone <15 ng/dL, renin >2 ng angiotensin I/mL/hr.
Interpretation: In pts w/primary aldosteronism, plasma aldosterone remains high and PRA remains low after captopril.

CARBON DIOXIDE, PARTIAL PRESSURE
Normal: 35-48 mm Hg (males); 32-45 mm Hg (females).
Elevated in: respiratory acidosis.
Decreased in: respiratory alkalosis.

CARBON MONOXIDE; see CARBOXYHEMOGLOBIN

CARBOXYHEMOGLOBIN
Normal range: saturation of Hgb <2%; smokers <9% (coma, 50%; death, 80%).
Elevated in: smoking, exposure to smoking, exposure to automobile exhaust fumes, malfunctioning gas-burning appliances.

CARCINOEMBRYONIC ANTIGEN (CEA)
Normal range: 0-2.5 ng/mL (nonsmokers); 0-5 ng/mL (smokers).
Elevated in: colorectal carcinomas, pancreatic carcinomas, and metastatic disease usually produce higher elevations (>20 ng/mL); carcinomas of the esophagus, stomach, small intestine, liver, breast, ovary, lung, and thyroid usually produce lesser elevations; benign conditions (smoking, IBD, hypothyroidism, cirrhosis, pancreatitis, infections) usually produce levels <10 ng/mL.

CARDIAC TROPONINS; see TROPONINS

CARDIO CRP; see C-REACTIVE PROTEIN

CAROTENE (Serum)
Normal range: 50-250 µg/dL.
Elevated in: carotenemia, chronic nephritis, DM, hypothyroidism, nephrotic syndrome, hyperlipidemia.
Decreased in: fat malabsorption, steatorrhea, pancreatic insufficiency, lack of carotenoids in diet, high fever, liver disease.

CATECHOLAMINES, URINE; see URINE CATECHOLAMINES

CBC; see COMPLETE BLOOD COUNT

CD4+ T-LYMPHOCYTE COUNT (CD4+ T Cells)
Calculated as total WBC × % lymphocytes × % lymphocytes stained w/CD4.
This test is used primarily to evaluate immune dysfunction in HIV infection and should be done every 3 to 6 months in all HIV-infected persons. It is useful as a prognostic indicator and as a criterion for initiation of prophylaxis for several opportunistic infections that are sequelae of HIV infection. Progressive depletion of CD4+ T lymphocytes is associated w/↑ likelihood of clinical complications. Adolescents and adults w/HIV infection are classified as having AIDS if their CD4+ lymphocyte count is below 200/µL or if their CD4+ T-lymphocyte percentage is <14%. HIV-infected pts whose CD4+ count is <200/µL and who acquire certain infectious diseases or malignant neoplasms are also classified as having AIDS. Corticosteroids ↓ CD4+ T-cell percentage and absolute number.

CD40 LIGAND
Normal: <5 µg/L. CD40 ligand is a soluble protein that is shed from activated leukocytes and platelets and used in risk stratification for ACS.
Elevated in: ACS. Increased CD40 ligand is associated w/higher incidence of death or nonfatal MI.
CEA; see CARCINOEMBRYONIC ANTIGEN

CERULOPLASMIN (Serum)
Normal range: 20-35 mg/dL.
Elevated in: pregnancy, estrogens, oral contraceptives, neoplastic diseases (leukemias, Hodgkin’s lymphoma, carcinomas), inflammatory states, SLE, PBC, RA.
Decreased in: Wilson’s disease (values often <10 mg/dL), nephrotic syndrome, advanced liver disease, malabsorption, TPN, Menkes’ syndrome.

CHLAMYDIA GROUP ANTIBODY SEROLOGIC TEST
Test description: Acute and convalescent serum samples are drawn 2 to 4 weeks apart. A fourfold increase in titer between acute and convalescent sera is necessary for confirmation. A single titer \( \geq 1:64 \) is considered indicative of psittacosis or lymphogranuloma venereum.

CHLORIDE (Serum)
Normal range: 95-105 mEq/L.
Elevated in: dehydration, sodium loss > chloride loss, respiratory alkalosis, excessive infusion of NS solution, cystic fibrosis, hyperparathyroidism, renal tubular disease, metabolic acidosis, prolonged diarrhea, acetazolamide administration, diabetes insipidus, ureterosigmoidostomy.
Decreased in: vomiting, gastric suction, primary aldosteronism, CHF, SIADH, Addison’s disease, salt-losing nephritis, continuous infusion of D\(_5\)W, thiazide diuretic administration, diaphoresis, diarrhea, burns, DKA.

CHLORIDE (Sweat)
Normal: 0-40 mmol/L.
Borderline/indeterminate: 41-60 mmol/L.
Consistent with cystic fibrosis: >60 mmol/L.
False low results can occur w/edema, excessive sweating, and hypoproteinemia.

CHLORIDE, URINE; see URINE CHLORIDE

CHOLESTEROL, LOW-DENSITY LIPOPROTEIN; see LOW-DENSITY LIPOPROTEIN CHOLESTEROL

CHOLESTEROL, HIGH-DENSITY LIPOPROTEIN; see HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

CHOLESTEROL, TOTAL
Normal range: Generally <200 mg/dL.
Elevated in: primary hypercholesterolemia, biliary obstruction, DM, nephrotic syndrome, hypothyroidism, PBC, diet high in cholesterol and total and saturated fat, third trimester of pregnancy, drugs (steroids, phenothiazines, oral contraceptives).
Decreased in: use of lipid-lowering agents (statins, niacin, ezetimibe, cholestyramine, colesevelam); starvation, malabsorption, abetalipoproteinemia, hyperthyroidism; hepatic failure, carcinoma, infection, inflammation.

CHORIONIC GONADOTROPINS, HUMAN (Serum)
Normal range, serum: <0.8 IU/L (female, premenopausal); <3.3 IU/L (female, postmenopausal); <0.7 IU/L (male).
Elevated in: pregnancy, choriocarcinoma, gestational trophoblastic neoplasia (including molar gestations), placental site trophoblastic tumors; human antimouse antibodies (HAMA) can produce false serum assay for hCG.
The principal use of this test is to diagnose pregnancy. The concentration of hCG increases significantly during the initial 6 weeks of pregnancy. Peak values approaching 100,000 IU/L occur 60 to 70 days after implantation.
hCG levels generally double every 1 to 3 days. In pts w/concentration <2000 IU/L, an increase of serum hCG <66% after 2 days is suggestive of spontaneous abortion or ruptured ectopic gestation.

**CHYMOTRYPsin**

**Normal:** <10 mcg/L.

**Elevated in:** acute pancreatitis, chronic renal failure, oral enzyme preparations, gastric cancer, pancreatic cancer.

**Decreased in:** chronic pancreatitis, late cystic fibrosis.

**CIRCULATING ANTICOAGULANT (Antiphospholipid Antibody, Lupus Anticoagulant)**

**Normal:** negative.

**Detected in:** SLE, drug-induced lupus, long-term phenothiazine Rx, MM, UC, RA, post partum, hemophilia, neoplasms, chronic inflammatory states, AIDS, nephrotic syndrome.

**Note:** The name is a misnomer because these pts are prone to hypercoagulability and thrombosis.

**CK; see** **CREATINE KINASE**

**CLONIDINE SUPPRESSION TEST**

**Interpretation:** Clonidine inhibits neurogenic catecholamine release and will cause a decrease in plasma norepinephrine into the reference interval in hypertensive subjects w/o pheochromocytoma. The test is performed by giving 4.3 μg clonidine/kg PO after an overnight fast. Norepinephrine is measured at 3 hours. The result should be within established reference range and decrease to <50% of baseline concentration. Lack of decrease in norepinephrine is suggestive of pheochromocytoma.

**CLOSTRIDIUM DIFFICILE TOXIN ASSAY (Stool)**

**Normal:** negative.

**Detected in:** abx-associated diarrhea and pseudomembranous colitis.

**CO; see** **CARBOXYHEMOGLOBIN**

**COAGULATION FACTORS**

**Factor reference ranges:**
- V: >10%
- VII: >10%
- VIII: 50%-170%
- IX: 60%-136%
- X: >10%
- XI: 50%-150%
- XII: >30%

**Figure 1-6** illustrates the blood coagulation pathways.

**COLD AGGLUTININS TITER**

**Normal range:** <1:32.

**Elevated in:** primary atypical pneumonia (Mycoplasma pneumonia), infectious mononucleosis, CMV infection, others (hepatic cirrhosis, acquired hemolytic anemia, frostbite, MM, lymphoma, malaria).

**COMPLEMENT (C3, C4)**

**Normal range:**
- C3: 70-160 mg/dL
- C4: 20-40 mg/dL

**Abnormal values:**
- Decreased C3: active SLE, immune complex disease, AGN, inborn C3 deficiency, membranoproliferative GN, infective endocarditis, serum sickness, autoimmune-type chronic active hepatitis.
- Decreased C4: immune complex disease, active SLE, infective endocarditis, inborn C4 deficiency, hereditary angioedema, hypergammaglobulinemic states, cryoglobulinemic vasculitis.
FIGURE 1-6. Coagulation cascade. Fibrin clot formation results from the generation of thrombin, which is dependent on the sequential interaction of proenzymes and activated coagulation factors in the intrinsic, extrinsic, and common pathways of coagulation. FDP, fibrin degradation product; HMW, high molecular weight; PL, phospholipid; TF, tissue factor; TPA, tissue plasminogen activator.

**COMPLETE BLOOD COUNT**

**WBCs:** 3200-9800/mm³

**RBCs:** 4.3-5.9 \(10^6/mm³\) (male); 3.5-5.0 \(10^6/mm³\) (female)

**Hgb:** 13.6-17.7 g/dL (male); 12-15 g/dL (female)

**Hct:** 39%-49% (male); 33%-43% (female)

**MCV:** 76-100 µm³

**MCH:** 27-33 pg

**MCHC:** 33-37 g/dL

**RDW:** 11.5%-14.5%

**Platelet count:** 130-400 × 10³/mm³

**Diff:** 2-6 bands (early mature neutrophils); 60-70 segs (mature neutrophils); 1-4 eosinophils; 0-1 basophils; 2-8 monocytes; 25-40 lymphocytes

**CONJUGATED BILIRUBIN:** see **BILIRUBIN, DIRECT**

**COOMBS, DIRECT (Antiglobulin Test, Direct, DAT)**

**Normal:** negative.

**Positive:** AIHA, erythroblastosis fetalis, transfusion reactions, drugs (methyldopa, PCNs, tetracycline, sulfonamides, levodopa, cephalosporins, quinidine, insulin).

**False positive:** may be seen w/cold agglutinins.

**COOMBS, INDIRECT**

**Normal:** negative.

**Positive:** acquired hemolytic anemia, incompatible crossmatched blood, anti-Rh antibodies, drugs (methyldopa, mefenamic acid, levodopa).

**COPPER (Serum)**

**Normal range:** 70-140 µg/dL.

**Decreased in:** Wilson’s disease, malabsorption, malnutrition, nephrosis, TPN, acute leukemia in remission.

**Elevated in:** aplastic anemia, biliary cirrhosis, SLE, hemochromatosis, hyperthyroidism, hypothyroidism, infection, iron deficiency anemia, leukemia, lymphoma, oral contraceptives, pernicious anemia, RA.
CORTICOTROPIN-RELEASING HORMONE (CRH) STIMULATION TEST

Normal: A dose of 0.5 mg of dexamethasone is given every 6 hours for 2 days; 2 hours after the last dose, 1 µg/kg CRH is given IV. Samples are drawn after 15 minutes. There is normally a twofold to fourfold increase in mean baseline concentration of ACTH or cortisol. Cortisol >1.4 µg/L is virtually 100% specific and 100% diagnostic.

Normal or exaggerated response: pituitary Cushing’s disease.

No response: ectopic ACTH-secreting tumor.

A positive response to CRH or a suppressed response to high-dose dexamethasone has a 97% positive predictive value for Cushing’s disease. However, a lack of response to either test excludes Cushing’s disease in only 64% to 78% of patients. When the tests are considered together, negative responses from both have a 100% predictive value for ectopic ACTH secretion.

CORTISOL (Plasma)

Normal range: varies w/ time of collection (circadian variation):
- 8 AM: 4-19 µg/dL
- 4 PM: 2-15 µg/dL

Elevated in: ectopic ACTH production (i.e., oat cell carcinoma of lung), loss of nl diurnal variation, pregnancy, chronic renal failure, iatrogenic, stress, adrenal or pituitary hyperplasia or adenomas.

Decreased in: primary adrenocortical insufficiency, anterior pituitary hypofunction, secondary adrenocortical insufficiency, adrenogenital syndromes.

C-PEPTIDE

Normal range (serum): 0.51-2.70 ng/mL.
Elevated in: insulinoma, sulfonylurea administration, type 2 DM, renal failure.
Decreased in: type 1 DM, factitious insulin administration.

CPK; see CREATINE KINASE

C-REACTIVE PROTEIN (CRP)

Normal range: <1 mg/dL. CRP levels are valuable in the clinical assessment of chronic inflammatory disorders such as RA, SLE, vasculitis syndromes, and IBD.

Elevated in: inflammatory and neoplastic diseases, MI, third trimester of pregnancy (acute-phase reactant), oral contraceptives. Moderately high CRP concentrations (3-10 mg/L) predict increased risk of MI and stroke. Markedly high levels (>10 mg/L) have been shown to predict CV risk.

Note: high-sensitivity C-reactive protein (hs-CRP, Cardio CRP) is used as a cardiac risk marker. It is ↑ in pts w/silent atherosclerosis for a prolonged period before a CV event and is independent of cholesterol level and other lipoproteins. It can be used to help stratify cardiac risk.

Interpretation of results: Table 1-8.

<table>
<thead>
<tr>
<th>TABLE 1-8</th>
<th>C-Reactive Protein: Interpretation of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio CRP Level (mg/L)</td>
<td>Risk</td>
</tr>
<tr>
<td>&lt;0.6</td>
<td>Lowest risk</td>
</tr>
<tr>
<td>0.7-1.1</td>
<td>Low risk</td>
</tr>
<tr>
<td>1.2-1.9</td>
<td>Moderate risk</td>
</tr>
<tr>
<td>2.0-3.8</td>
<td>High risk</td>
</tr>
<tr>
<td>3.9-4.9</td>
<td>Highest risk</td>
</tr>
<tr>
<td>&gt;5.0</td>
<td>Results may be confounded by acute inflammatory disease. If clinically indicated, a test should be repeated in 2 weeks or more.</td>
</tr>
</tbody>
</table>
CREATINE KINASE (CK, CPK)

**Normal range:** 0–130 U/L.

**Elevated in:** vigorous exercise, IM injections, MI, myocarditis, rhabdo, myositis, crush injury or trauma, polymyositis, dermatomyositis, muscular dystrophy, myxedema, seizures, malignant hyperthermia syndrome, CVA, pulmonary embolism and infarction, acute dissection of aorta.

**Decreased in:** steroids, decreased muscle mass, connective tissue disorders, alcoholic liver disease, metastatic neoplasms.

CREATINE KINASE ISOENZYMES

**CK-MB**

**Elevated in:** MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, cardiac surgery, extensive rhabdo, strenuous exercise [e.g., marathon runners], MCTD, cardiomyopathy, hypothermia.

**Note:** CK-MB exists in the blood in two subforms. MB2 is released from cardiac cells and converted in the blood to MB1. Rapid assay of CK-MB subforms can detect MI (CK-MB2 ≥ 1.0 U/L, w/a ratio of CK-MB2/CK-MB1 ≥ 1.5) within the first 6 hours of onset of sx.

**CK-MM**

**Elevated in:** crush injury, seizures, malignant hyperthermia syndrome, rhabdo, myositis, polymyositis, dermatomyositis, vigorous exercise, muscular dystrophy, IM injections, acute dissection of aorta.

**CK-BB**

**Elevated in:** CVA, subarachnoid hemorrhage, neoplasms (prostate, GI tract, brain, ovary, breast, lung), severe shock, bowel infarction, hypothermia, meningitis.

CREATININE (Serum)

**Normal range:** 0.6–1.2 mg/dL.

**Elevated in:** renal insufficiency (acute and chronic), decreased renal perfusion (hypotension, dehydration, CHF), rhabdo, administration of contrast dyes, ketonemia, drugs [abx [AGs, cephalosporins], ACEIs [in pts w/RAS], diuretics).

**Falsely elevated in:** DKA, administration of some cephalosporins (e.g., cefoxitin, cephalothin).

**Decreased in:** decreased muscle mass (including amputees and elderly), pregnancy, prolonged debilitation.

CREATININE CLEARANCE

**Normal range:** 75–124 mL/min.

**Elevated in:** pregnancy, exercise.

**Decreased in:** renal insufficiency, drugs (e.g., cimetidine, procainamide, abx, quinidine).

CREATININE, URINE; see URINE CREATININE

CRYOGLOBULINS (Serum)

**Normal range:** not detectable.

**Present in:** collagen-vascular diseases, chronic active hepatitis, CLL, hemolytic anemias, MM, Waldenström’s macroglobulinemia, Hodgkin’s disease.

CRYPTOSPORIDIUM ANTIGEN BY EIA (Stool)

**Normal range:** not detected.

**Present in:** cryptosporidiosis.

CYSTATIN C

**Normal:** Cystatin C is a cysteine protease inhibitor that is produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus and reabsorbed (but not secreted) by the renal tubules w/no extrarenal excretion. Its concentration is not affected by diet, muscle mass, or acute inflammation. NI range when measured by particle-enhanced nephelometric immunoassay (PENIA) is <0.28 mg/L.
**Elevated in:** renal disorders; good predictor of the severity of ATN. Cystatin C \( \uparrow \) more rapidly than Cr in the early stages of GFR impairment. The cystatin C concentration is an independent risk factor for heart failure in older adults and appears to provide a better measure of risk assessment than the serum Cr concentration.

**CYSTIC FIBROSIS PCR**

**Test description:** The test can be performed on whole blood or tissue. Common mutations in the cystic fibrosis transmembrane regulator (CFTR) gene can be used to detect 75% to 80% of mutant alleles.

**CYTOMEGALOVIRUS BY PCR**

**Test description:** The test can be performed on whole blood, plasma, or tissue. Qualitative PCR is highly sensitive but may not be able to differentiate between latent and active infection.

**D-DIMER**

**Normal range:** <0.5 µg/mL.

**Elevated in:** DVT, PE, high levels of RF, activation of coagulation and fibrinolytic systems from any cause.

D-dimer assay by ELISA assists in the dx of DVT and PE. This test has significant limitations because it can be elevated whenever the coagulation and fibrinolytic systems are activated and can also be falsely elevated w/high RF levels.

**DEHYDROEPIANDROSTERONE SULFATE**

**Normal:**
- **Males:**
  - Age 19-30: 125-619 µg/dL
  - Age 31-50: 59-452 µg/dL
  - Age 51-60: 20-413 µg/dL
  - Age 61-83: 10-285 µg/dL
- **Females:**
  - Age 19-30: 29-781 µg/dL
  - Age 31-50: 12-379 µg/dL
  - Postmenopausal: 30-260 µg/dL

**Elevated in:** hirsutism, congenital adrenal hyperplasia, adrenal carcinomas, adrenal adenomas, polycystic ovary syndrome, ectopic ACTH-producing tumors, Cushing’s disease, spironolactone.

**DEOXYCORTICOSTERONE (11-DEOXYCORTICOSTERONE, DOC) (Serum)**

**Normal:** 2-19 ng/dL; nl secretion is dependent on ACTH and is suppressible by dexamethasone.

**Elevated in:** androgenital syndromes due to 17- and 11-hydroxylase deficiencies, pregnancy.

**Decreased in:** preeclampsia.

**DEXAMETHASONE SUPPRESSION TEST, OVERNIGHT**

**Normal:** The test is performed by giving 1 mg dexamethasone PO at 11 PM and measuring serum cortisol at 8 AM on the following morning; nl response is cortisol suppression to <3 µg/dL. If dose of 4 mg dexamethasone is given, cortisol suppression will be to <50% of baseline.

**Interpretation:** Cushing’s syndrome (>10 µg/dL), endogenous depression (half of pts suppress test values >5 µg/dL). Most pts w/pituitary Cushing’s disease demonstrate suppression, whereas pts w/adrenal adenoma, carcinoma, and ectopic ACTH-producing tumors do not.

**DIGOXIN (LANOXIN)**

**Normal therapeutic range:** 0.5-2 ng/mL.

**Elevated in:** impaired renal function, excessive dosing; concomitant use of quinidine, amiodarone, verapamil, fluoxetine, nifedipine.
DIHYDROTESTOSTERONE (Serum, Urine)

Normal:
- Serum: 30-85 ng/dL (males); 4-22 ng/dL (females)
- Urine, 24-hour: 20-50 µg/dL (males); <8 µg/day (females)

Elevated in: hirsutism.
Decreased in: 5α-reductase deficiency, hypogonadism.

DISACCHARIDE ABSORPTION TESTS

Normal: The test is used to diagnose malabsorption due to disaccharide deficiency. It is performed by giving disaccharide PO 1 g/kg BW to a total of 25 g. Blood is drawn at 0, 30, 60, 90, and 120 minutes. NI response is a change in glucose concentration from fasting value >30 mg/dL, inconclusive when ↑ is 20 to 30 mg/dL, abnl when ↑ is <20 mg/dL. The test can also be performed by measuring air at 0, 30, 60, 90, and 120 minutes. NI is H₂ >20 ppm above baseline level before a colonic response.

Decreased in: disaccharide deficiency (lactose, fructose, sorbitol), celiac disease, sprue, acute gastroenteritis.

DOC; see DEOXYCORTICOSTERONE

DONATH-LANDSTEINER (D-L) TEST FOR PAROXYSMAL COLD HEMOGLOBINURIA

Normal: no hemolysis.
Interpretation: hemolysis indicates presence of bithermic cold hemolysins or Donath-Landsteiner antibodies (D-L Ab).

DOPAMINE

Normal range: 0-175 pg/mL.
Elevated in: pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla).

ELECTROPHORESIS, HEMOGLOBIN; see HEMOGLOBIN ELECTROPHORESIS

ELECTROPHORESIS, PROTEIN; see PROTEIN ELECTROPHORESIS

ENA COMPLEX; see EXTRACTABLE NUCLEAR ANTIGEN

ENDOMYSIAL ANTIBODIES

Normal: not detected.
Present in: celiac disease, dermatitis herpetiformis.

EOSINOPHIL COUNT

Normal range: 1%-4% eosinophils (0-440/mm³).
Elevated in: allergy, parasitic infestations (trichinosis, aspergillosis, hydatidosis), angioneurotic edema, drug reactions, warfarin sensitivity, collagen-vascular diseases, acute hypereosinophilic syndrome, eosinophilic nonallergic rhinitis, myeloproliferative disorders, Hodgkin's lymphoma, radiation Rx, NHL, L-tryptophan ingestion, urticaria, pernicious anemia, pemphigus, IBD, bronchial asthma.

EPINEPHRINE (Plasma)

Normal range: 0-90 pg/mL.
Elevated in: pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla), hypoglycemia.

EPSTEIN-BARR VIRUS SEROLOGY

Normal range:
- IgG anti-VCA <1:10 or negative
- IgM anti-VCA<1:10 or negative
- Anti-EBNA <1:5 or negative
Abnormal:
- IgG anti-VCA >1:10 or positive indicates either current or previous infection.
- IgM anti-VCA >1:10 or positive indicates current or recent infection.
- Anti-EBNA ≥1.5 or positive indicates previous infection.

ERYTHROCYTE SEDIMENTATION RATE (ESR) (Westergren)
Normal range: 0-15 mm/hr (male); 0-20 mm/hr (female).
Elevated in: inflammatory states (acute-phase reactant), collagen-vascular diseases, infections, MI, neoplasms, hyperthyroidism, hypothyroidism, rouleaux formation, elderly, pregnancy.
Note: Sedimentation rates >100 mm/hr are strongly associated w/serious underlying disease (collagen-vascular, infection, malignant disease). Some clinicians use ESR as a “sickness index”; high rates encountered w/o obvious reason should be repeated rather than pursuing extensive search for occult disease.
Decreased in: sickle cell disease, polycythemia, corticosteroids, spherocytosis, anisocytosis, hypofibrinogenemia, ↑ serum viscosity, microcytosis.

ERYTHROPOIETIN
Normal: 3.7-16.0 IU/L by radioimmunoassay. Erythropoietin is a glycoprotein secreted by the kidneys that stimulates RBC production by acting on erythroid committed stem cells.
Increased in:
- Extremely high: generally seen in pts w/severe anemia (Hct <25, Hgb <7), such as in cases of aplastic anemia, severe hemolytic anemia, hematologic cancers.
- Very high: pts w/mild to moderate anemia (Hct 25-35, Hgb 7-10).
- High: patient w/mild anemia (e.g., AIDS, myelodysplasia).
Erythropoietin can be inappropriately elevated in pts w/malignant neoplasms, renal cysts, post–renal transplantation, meningioma, hemangioblastoma, and leiomyoma.
Decreased in: renal failure, PV, autonomic neuropathy.

ESTRADIOL (Serum)
Normal range:
- Female, premenopausal: 30-400 pg/mL (depending on phase of menstrual cycle)
- Female, postmenopausal: 0-30 pg/mL
- Male, adult: 10-50 pg/mL
Decreased in: ovarian failure.
Elevated in: tumors of ovary, testis, adrenal, or nonendocrine sites (rare).

ESTROGENS, TOTAL
Normal:
- Female: 60-200 pg/mL (follicular phase); 160-400 pg/mL (luteal phase); <130 pg/mL (postmenopausal)
- Male: 20-80 pg/mL
Elevated in: ovarian tumor producing estrogens, testicular tumors, tumors or hyperplasia of adrenal cortex, chorioepithelioma.
Decreased in: menopause, primary ovarian failure, hypopituitarism, anorexia nervosa, GnRH deficiency, psychogenic stress.

ETHANOL (Blood)
Normal range: negative (values <10 mg/dL are considered negative). Ethanol is metabolized at 10-25 mg/dL/hr. Levels ≥80 mg/dL are considered evidence of impairment for driving. Fatal blood concentration is considered to be >400 mg/dL, although levels >400 mg/dL may be seen in chronic alcoholics.
**EXTRACTABLE NUCLEAR ANTIGEN (ENA Complex, Anti-RNP Antibody, Anti-Sm, Anti-Smith)**

**Normal:** negative.
**Present in:** SLE, RA, Sjögren’s syndrome, MCTD.

**FACTOR V LEIDEN**

**Test description:** PCR test is performed on whole blood or tissue. This single mutation, found in 2% to 8% of the general white population, is the single most common cause of hereditary thrombophilia.

**FBS; see GLUCOSE, FASTING**

**FDP; see FIBRIN DEGRADATION PRODUCT**

**FECAL FAT, QUALITATIVE; see SUDAN III STAIN**

**FECAL FAT, QUANTITATIVE (72-Hour Collection)**

**Normal range:** 2-6 g/24 hr.
**Elevated in:** malabsorption syndrome.

**FECAL GLOBIN IMMUNOCHEMICAL TEST**

**Normal:** negative. This test is performed by immunochromatography on a cellulose strip that has been impregnated w/various antibodies. The test uses a small amount of toilet water as the specimen, which is placed onto absorbent pads of card similar to traditional OB card. There is no direct handling of stool. This test is specific for the globin portion of the Hgb molecule that confers lower GI bleeding specificity. It specifically detects blood from lower GI tract; guaiac tests are not lower GI specific. It is more sensitive than the typical hemoccult test (detection limit 50 µg Hgb/g feces versus >500 µg Hgb/g feces for hemoccult). It has no dietary restrictions and gives no false-positive results from plant peroxidases and red meats. It has no medication restrictions. Iron supplements and NSAIDs do not cause false-positive results. Vitamin C does not cause false-negative results.
**Positive in:** lower GI bleeding.

**FERRITIN (Serum)**

**Normal range:** 18-300 ng/mL.
**Elevated in:** inflammatory states, liver disease (ferritin elevated from necrotic hepatocytes), hyperthyroidism, neoplasms (neuroblastomas, lymphomas, leukemia, breast carcinoma), iron replacement Rx, hemochromatosis, hemosiderosis.
**Decreased in:** iron deficiency anemia.

**FIBRIN DEGRADATION PRODUCT (FDP)**

**Normal range:** <10 µg/mL.
**Elevated in:** DIC, primary fibrinolysis, PE, severe liver disease.
**Note:** The presence of RF may cause falsely elevated FDP.

**FIBRINOGEN**

**Normal range:** 200-400 mg/dL.
**Elevated in:** tissue inflammation or damage (acute-phase protein reactant), oral contraceptives, pregnancy, acute infection, MI.
**Decreased in:** DIC, hereditary afibrinogenemia, liver disease, primary or secondary fibrinolysis, cachexia.

**FLUORESCENT TREponemAL antiboDY; see FTA-ABS**

**FOLATE (Folic Acid)**

**Normal range:**
- Plasma: <3.4 ng/mL (low); >5.4 ng/mL (nl)
- RBC: >280 ng/mL
Decreased in: folic acid deficiency (inadequate intake, malabsorption), alcoholism, drugs (MTX, trimethoprim, phenytoin, oral contraceptives, sulfasalazine), vitamin B₁₂ deficiency (defective red cell folate absorption), hemolytic anemia.

Elevated in: folic acid Rx.

FOLLICLE-STIMULATING HORMONE (FSH)

Normal range:
- Female, adult: <40 IU/L (midcycle); <20 IU/L (non-midcycle); 40-160 IU/L (postmenopausal)
- Male, adult: <22 IU/L

Elevated in: primary hypogonadism, gonadal failure, alcoholism, Klinefelter’s syndrome, testicular feminization, anorchia, castration.

Decreased in: precocious puberty related to adrenal tumors, congenital adrenal hyperplasia. NI FSH in adult nonovulating female is indicative of hypopthalamic or pituitary dysfunction.

FREE T₄; see T₄, FREE

FREE THYROXINE INDEX

Normal range: 1.1-4.3.

Serum free T₄ directly measures unbound thyroxine. Free T₄ can be measured by equilibrium dialysis (gold standard of free T₄ assays) or by immunometric techniques (influenced by serum levels of lipids, proteins, and certain drugs). The FTI can also be easily calculated by multiplying T₄ times T₃RU and dividing the result by 100; the FTI corrects for any abnl T₄ values secondary to protein binding: FTI = T₄ × T₃RU/100.

FSH; see FOLLICLE-STIMULATING HORMONE

FTA-ABS (Serum)

Normal: nonreactive.

Reactive in: syphilis, other treponemal diseases (yaws, pinta, bejel), SLE, pregnancy.

FUROSEMIDE STIMULATION TEST

Normal: The test is performed by giving 60 mg furosemide PO after overnight fast. Patient should be on a nl diet w/o medications the week before the test. NI results: renin 1-6 ng angiotensin I/ml/hr.

Elevated in: renovascular HTN, Bartter’s syndrome, high-renin essential HTN, pheochromocytoma.

No response in: primary aldosteronism, low-renin essential HTN, hyporeninemic hypoaldosteronism.

GAMMA-GLUTAMYLTRANSFERASE (GGT); see γ-GLUTAMYLTRANSFERASE

GASTRIN (Serum)

Normal range: 0-180 pg/mL.

Elevated in: Zollinger-Ellison syndrome (gastrinoma), use of PPIs, chronic renal failure, gastric ulcer, chronic atrophic gastritis, pyloric obstruction, malignant neoplasms of the stomach, H₂ blockers, Ca Rx, UC, RA.

GASTRIN STIMULATION TEST

Normal: Gastrin stimulation test after Ca infusion is performed by giving a Ca infusion (15 mg Ca/kg in 500 mL NS during 4 hours). Serum is drawn in fasting state before infusion and at 1, 2, 3, and 4 hours. NI response is little or no increase over baseline gastrin level.

Elevated in: gastrinoma (gastrin >400 pg/mL), duodenal ulcer (gastrin level increase <400 ng/L).

Decreased in: pernicious anemia, atrophic gastritis.
GH; see GROWTH HORMONE

GHRH; see GROWTH HORMONE–RELEASING HORMONE

GLIADIN ANTIBODIES, IGA AND IGG

Normal: <25 U; equivocal, 20-25 U; positive, >25 U. The test is useful to monitor compliance w/gluten-free diet in pts w/celiac disease.

Elevated in: celiac disease w/dietary noncompliance.

GLOMERULAR BASEMENT MEMBRANE ANTIBODY

Normal: negative.

Present in: Goodpasture’s syndrome.

GLOMERULAR FILTRATION RATE

Normal:

- Age 20-29: 116 mL/min/1.73 m²
- Age 30-39: 107 mL/min/1.73 m²
- Age 40-49: 99 mL/min/1.73 m²
- Age 50-59: 93 mL/min/1.73 m²
- Age 60-69: 85 mL/min/1.73 m²
- Age ≥70: 75 mL/min/1.73 m²

Decreased in: renal insufficiency, ↓ renal blood flow.

GLUCAGON

Normal: 20-100 pg/mL.

Elevated in: glucagonoma (900–7800 pg/mL), chronic renal failure, DM, glucocorticoids, insulin, nifedipine, danazol, sympathomimetic amines.

Decreased in: hyperlipoproteinemia (types III, IV), β-blockers, secretin.

GLUCOSE, FASTING (Fasting Blood Sugar, FBS)

Normal range: 60-99 mg/dL.

Elevated in: DM, stress, infections, MI, CVA, Cushing’s syndrome, acromegaly, acute pancreatitis, glucagonoma, hemochromatosis, drugs (glucocorticoids, diuretics [thiazides, loop diuretics]), impaired glucose tolerance.

Decreased in: prolonged fasting, excessive dose of insulin or hypoglycemic agents, insulinoma.

GLUCOSE, POSTPRANDIAL

Normal range: <140 mg/dL.

Elevated in: DM, impaired glucose tolerance.

Decreased in: post–gastrointestinal resection, reactive hypoglycemia, hereditary fructose intolerance, galactosemia, leucine sensitivity.

GLUCOSE TOLERANCE TEST

Normal values above fasting:

- 30 minutes: 30-60 mg/dL
- 60 minutes: 20-50 mg/dL
- 120 minutes: 5-15 mg/dL
- 180 minutes: fasting level or below

Abnormal in: impaired glucose tolerance, DM, Cushing’s syndrome, acromegaly, pheochromocytoma, gestational diabetes.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE SCREEN (Blood)

Normal: G6PD enzyme activity is detected.

Abnormal: If a deficiency is detected, quantitation of G6PD is necessary; a G6PD screen may be falsely interpreted as “normal” after an episode of hemolysis because most G6PD-deficient cells have been destroyed.

γ-GLUTAMYLTRANSFERASE (GGT)

Normal range: 0–30 U/L.

Elevated in: chronic alcoholic liver disease, neoplasms (hepatoma, metastatic disease to the liver, carcinoma of the pancreas), nephrotic syndrome, sepsis, cholestasis, drugs (phenytoin, barbiturates).
Chapter 1  Surviving the Wards

GLYCOHEMOGLOBIN (HbA1c, Glycated Hemoglobin, Glycosylated Hemoglobin)

Normal range: 4.0%-6.0% (Table 1-9).

Elevated in: uncontrolled DM (glycated Hgb levels reflect the level of glucose control during the preceding 120 days), lead toxicity, alcoholism, iron deficiency anemia, hypertriglyceridemia.

Decreased in: hemolytic anemias, decreased RBC survival, pregnancy, acute or chronic blood loss, chronic renal failure, insulinoma, congenital spherocytosis; HbS, HbC, HbD diseases.

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GROWTH HORMONE (GH)

Normal: 1-9 ng/mL (male); 1-16 ng/mL (female).


Decreased in: hypopituitarism, pituitary dwarfism, adrenocortical hyperfunction, bromocriptine, corticosteroids, glucose.

GROWTH HORMONE–RELEASING HORMONE (GHRH)

Normal: <50 pg/mL.

Elevated in: acromegaly caused by GHRH secretion by neoplasms.

GROWTH HORMONE SUPPRESSION TEST (After Glucose)

Normal: The test is done by giving 1.75 g glucose/kg PO after overnight fast. Blood is drawn at baseline and after 60 minutes and after 120 minutes of glucose load. NI response is GH suppression to <2 ng/mL or undetectable levels.

Abnormal: There is no or incomplete suppression from the high basal level in gigantism or acromegaly.

HAPTOGLOBIN (Serum)

Normal range: 50-220 mg/dL.

Elevated in: inflammation (acute-phase reactant), collagen-vascular diseases, infections (acute-phase reactant), drugs (androgens), obstructive liver disease.

Decreased in: hemolysis (intravascular more than extravascular), megaloblastic anemia, severe liver disease, large tissue hematomas, infectious mononucleosis, drugs (oral contraceptives).

HDL; see HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

HELCOBACTER PYLORI (Serology, Stool Antigen)

Normal range: not detected.

Detected in: H. pylori infection. Positive serology can indicate current or past infection. Positive stool antigen test result indicates acute infection (sensitivity and specificity >90%). Stool testing should be delayed at least 2 weeks after eradication Rx.
HEMATOCRIT
Normal range: 39%-49% (male); 33%-43% (female).
Elevated in: PV, smoking, COPD, high altitudes, dehydration, hypovolemia.
Decreased in: blood loss (GI, GU), anemia, pregnancy.

HEMOGLOBIN
Normal range: 13.6-17.7 g/dL (male); 12.0-15.0 g/dL (female).
Elevated in: hemoconcentration, dehydration, PV, COPD, high altitudes, false elevations (hyperlipemic plasma, WBCs >50,000 mm³), stress.
Decreased in: hemorrhage (GI, GU), anemia.

HEMOGLOBIN ELECTROPHORESIS
Normal range:
- HbA1: 95%-98%
- HbA2: 1.5%-3.5%
- HbF: <2%
- HbC: absent
- Hbs: absent

HEMOGLOBIN, URINE; see URINE HEMOGLOBIN

HEMOSIDERIN, URINE; see URINE HEMOSIDERIN

HEPARIN-INDUCED THROMBOCYTOPENIA ANTIBODIES
Normal: antigen assay: negative, <0.45; weak, 0.45-1.0; strong, >1.0.
Elevated in: HIT.

HEPATITIS A ANTIBODY
Normal: negative.
Present in: viral hepatitis A; can be IgM or IgG (if IgM, acute hepatitis A; if IgG, previous infection w/hepatitis A).

HEPATITIS B ANTIGEN AND ANTIBODY
Normal: negative. These tests are ordered together and should be used only in pts who are chronically HBsAg positive. The main utility of these tests is to assess response of hepatitis B infection to Rx.
Present in: Presence of HBeAg implies that infective HBV is present in serum. However, its absence on conversion to anti-HBe does not rule out infectivity, especially in persons infected w/genotypes other than A. Measurement of HBV DNA is useful in persons w/↑ ALT but negative HBeAg.

HEPATITIS B CORE ANTIBODY
Normal: negative.
Present in: hepatitis B. Anti-HBc assay is the first Ab test to become positive w/exposure to HBV and persists the longest after resolution of acute infection.

HEPATITIS B DNA
Normal: negative.
Present in: active hepatitis B infection. It implies infectivity of the serum. Currently used to assess response of hepatitis B to Rx.

HEPATITIS B SURFACE ANTIBODY
Normal: negative.
Present in: post-vaccination for hepatitis B (a level >10 U/L for post-vaccine testing is the accepted concentration that indicates protection), post-infection w/hepatitis B (it generally appears several weeks after disappearance of HBsAg).

HEPATITIS B SURFACE ANTIGEN (HBsAG)
Normal: not detected.
Detected in: acute viral hepatitis type B, chronic hepatitis B.
HEPATITIS C ANTIBODY (Anti-HCV)

Normal: negative.
Present in: hepatitis C. CDC guidelines recommend confirmation w/RIBA before reporting of anti-HCV as positive. HCV RNA can also be obtained if there is a high clinical suspicion of HCV despite a negative anti-HVC, especially in immunosuppressed individuals or in the setting of acute hepatitis. Anti-HCV and the RIBA often do not become positive during an acute infection; thus, repeated testing several months later is required if HCV RNA is negative.

HEPATITIS C RNA

Normal: negative.
Elevated in: hepatitis C. Detection of hepatitis C RNA is used to confirm current infection and to monitor treatment. Quantitative assays (viral load) are needed before treatment to assess response (<2 log ↓ after 12-week treatment indicates lack of response).

HEPATITIS DELTA ANTIGEN AND ANTIBODY

Normal: negative.
Elevated in: hepatitis delta. Hepatitis delta is a replication-defective RNA virus that requires the surface coat of hepatitis B (HBsAg) to become an infectious virus. Testing for hepatitis delta is therefore done only in pts positive for HBsAg. It is useful in pts w/chronic hepatitis B if there is an exacerbation of stable hepatitis.

HER-2/neu

Normal: negative.
Present in: 25%-30% of primary breast cancers. It can also be found in other epithelial tumors, including lung, hepatocellular, pancreatic, colon, stomach, ovarian, cervical, and bladder cancer. Trastuzumab (Herceptin) is a humanized monoclonal Ab against Her-2/neu. The test is useful to identify pts w/metastatic, recurrent, or treatment-refractory unresectable locally advanced breast cancer for trastuzumab treatment.

HETEROPHILE ANTIBODY


HFE SCREEN FOR HEREDITARY HEMOCROMATOSIS

Test description: PCR test can be performed on whole blood or tissue. One mutation (C282Y) and two polymorphisms (H63D, S65C) account for the majority of alleles associated w/this disease.

HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL

Normal range: 45-70 mg/dL (male); 50-90 mg/dL (female).
Increased in: use of fenofibrate, gemfibrozil, nicotinic acid, estrogens, regular aerobic exercise, mild to moderate (1-oz) daily EtOH intake.
Decreased in: familial deficiency of apoproteins, liver disease, probucol ingestion, sedentary lifestyle, acute MI, CVA, starvation.
Note: A cholesterol/HDL ratio ≥4.5 is associated w/↑ risk of CAD.

HOMOCYSTEINE (Plasma)

Normal range:
- 0-30 years: 4.6-8.1 µmol/L
- 30-59 years: 6.3-11.2 µmol/L (males); 4.5-7.9 µmol/L (females)
- >59 years: 5.8-11.9 µmol/L
Increased in: thrombophilic states; B₆, B₁₂, folic acid, riboflavin deficiency; pregnancy; homocystinuria.
Note: An increased homocysteine level is an independent risk factor for atherosclerosis.
hs-CRP; see C-REACTIVE PROTEIN

HUMAN IMMUNODEFICIENCY VIRUS ANTIBODY, TYPE 1 (HIV-1)

Normal range: not detected.
Abnormal result: HIV antibodies usually appear in the blood 1 to 4 months after infection.

Testing sequence:
1. ELISA is the recommended initial screening test. Sensitivity and specificity are >99%. False-positive ELISA results may occur with autoimmune disorders, administration of immune globulin manufactured before 1985 within 6 weeks of testing, presence of RF, presence of DLA-DR antibodies in multigravida woman, administration of influenz vaccine within 3 months of testing, hemodialysis, positive plasma reagin test response, and certain medical disorders (hemophilia, hypergammaglobulinemia, alcoholic hepatitis).
2. A positive ELISA result is confirmed with Western blot. False-positive Western blot may be caused by connective tissue disorders, human leukocyte antigen antibodies, polyclonal gammopathies, hyperbilirubinemia, presence of Ab to another human retrovirus, cross-reaction with other non–virus-derived proteins in healthy persons. Undetermined Western blot may occur in AIDS pts w/advanced immunodeficiency (from loss of antibodies) and in recent HIV infections.
3. PCR is used to confirm indeterminate Western blot results or negative results in persons w/suspected HIV infection.

5-HYDROXYINDOLEACETIC ACID, URINE; see URINE 5-HYDROXYINDOLEACETIC ACID

IMMUNE COMPLEX ASSAY

Normal: negative.
Detected in: collagen-vascular disorders, GN, neoplastic diseases, malaria, PBC, chronic acute hepatitis, bacterial endocarditis, vasculitis.

IMMUNOGLOBULINS

Normal range:
- IgA: 50-350 mg/dL
- IgD: <6 mg/dL
- IgE: <25 µg/dL
- IgG: 800-1500 mg/dL
- IgM: 45-150 mg/dL

Elevated in:
- IgA: lymphoproliferative disorders, Berger’s nephropathy, chronic infections, autoimmune disorders, liver disease.
- IgE: allergic disorders, parasitic infections, immunologic disorders, IgE myeloma, AIDS, pemphigoid.
- IgG: chronic granulomatous infections, infectious diseases, inflammation, myeloma, liver disease.
- IgM: PBC, infectious diseases (brucellosis, malaria), Waldenström’s macroglobulinemia, liver disease.

Decreased in:
- IgA: nephrotic syndrome, protein-losing enteropathy, congenital deficiency, lymphocytic leukemia, ataxia-telangiectasia, chronic sinopulmonary disease.
- IgE: hypogammaglobulinemia, neoplasm (breast, bronchial, cervical), ataxia-telangiectasia.
- IgG: congenital or acquired deficiency, lymphocytic leukemia, phenytoin, methylprednisolone, nephrotic syndrome, protein-losing enteropathy.
- IgM: congenital deficiency, lymphocytic leukemia, nephrotic syndrome.
**INR; see INTERNATIONAL NORMALIZED RATIO**

**INSULIN AUTOANTIBODIES**

**Normal:** negative.

**Present in:** exogenous insulin from insulin Rx. The presence of islet cell antibodies indicates ongoing beta cell destruction. This test is useful in the early dx of type IA DM and in the identification of pts at high risk for type IA diabetes.

**INSULIN, FREE**

**Normal:** <17 µU/mL.

**Elevated in:** insulin OD, insulin resistance syndromes, endogenous hyperinsulinemia.

**Decreased in:** inadequately treated type 1 DM.

**INSULIN-LIKE GROWTH FACTOR 1 (IGF-1) (Serum)**

**Normal range:**

- Age 16-24: 182-780 ng/mL
- Age 25-39: 114-492 ng/mL
- Age 40-54: 90-360 ng/mL
- Age >55: 71-290 ng/mL

**Elevated in:** adolescence, acromegaly, pregnancy, precocious puberty, obesity.

**Decreased in:** malnutrition, delayed puberty, DM, hypopituitarism, cirrhosis, old age.

**INSULIN-LIKE GROWTH FACTOR 2**

**Normal:** 288-736 ng/mL.

**Elevated in:** hypoglycemia associated w/non–islet cell tumors, hepatoma, and Wilms’ tumor.

**Decreased in:** GH deficiency.

**INTERNATIONAL NORMALIZED RATIO (INR)**

The INR is a comparative rating of PT ratios. The INR represents the observed PT ratio adjusted by the International Reference Sensitivity Index. INR = PT patient/PT mean. The INR provides a universal result indicative of what the patient’s PT result would have been if measured by use of the primary World Health Organization International Reference reagent. For proper interpretation of INR values, the patient should be on stable anticoagulant Rx. NI range of INR is 0.8-1.2

**Recommended INR ranges:** Table 1-10.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>INR Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal deep venous thrombosis</td>
<td>2-3</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2-3</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>2-3</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2-3</td>
</tr>
<tr>
<td>Mechanical prosthetic valves</td>
<td>3-4.5</td>
</tr>
<tr>
<td>Recurrent venous thromboembolic disease</td>
<td>3-4.5</td>
</tr>
</tbody>
</table>
INTRINSIC FACTOR ANTIBODIES
Normal: negative.
Present in: pernicious anemia (>50% of pts). Cyanocobalamin may give false-positive results.

IRON (Serum)
Normal: 65-175 μg/dL (male); 50-1170 μg/dL (female).
 Elevated in: hemochromatosis, excessive iron Rx, repeated transfusions, lead poisoning, hemolytic anemia, aplastic anemia, pernicious anemia.
 Decreased in: iron deficiency anemia, hypothyroidism, chronic infection.

IRON-BINDING CAPACITY (TIBC)
Normal range: 250-460 μg/dL.
 Elevated in: iron deficiency anemia, pregnancy, polycythemia, hepatitis, weight loss.
 Decreased in: anemia of chronic disease, hemochromatosis, chronic liver disease, hemolytic anemias, malnutrition (protein depletion).

IRON SATURATION (% Transferrin Saturation)
Normal: 20%-50% (male); 15%-50% (female).
 Elevated in: hemochromatosis, excessive iron intake, aplastic anemia, thalassemia, vitamin B₉ deficiency.
 Decreased in: hypochromic anemias, GI malignant disease.

LACTATE (Blood)
Normal range: 0.5-2.0 mEq/L.
 Elevated in: tissue hypoxia (shock, respiratory failure, severe CHF, severe anemia, CO or cyanide poisoning), systemic disorders (liver or renal failure, seizures), abnl intestinal flora (d-lactic acidosis), drugs or toxins (salicylates, ethanol, methanol, ethylene glycol), G6PD deficiency.

LACTATE DEHYDROGENASE (LDH)
Normal range: 50-150 U/L.
 Elevated in: infarction of myocardium, lung, kidney; diseases of cardiopulmonary system, liver, collagen, CNS; hemolytic anemias; megaloblastic anemias; transfusions; seizures; muscle trauma; muscular dystrophy; acute pancreatitis; hypotension; shock; infectious mononucleosis; inflammation; neoplasia; intestinal obstruction; hypothyroidism.

LACTATE DEHYDROGENASE ISOENZYMES
Normal range:
- LDH₁: 22%-36% (cardiac, RBCs)
- LDH₂: 55%-46% (cardiac, RBCs)
- LDH₃: 13%-26% (pulmonary)
- LDH₄: 3%-10% (striated muscle, liver)
- LDH₅: 2%-9% (striated muscle, liver)

Normal range:
- LDH₁ < LDH₂
- LDH₅ < LDH₄

Abnormal values:
- LDH₁ > LDH₂: MI (can also be seen w/hemolytic anemias, pernicious anemia, folate deficiency, renal infarct)
- LDH₅ > LDH₄: liver disease (cirrhosis, hepatitis, hepatic congestion)

LACTOSE TOLERANCE TEST (Serum)
Normal: The test is performed by giving 2 g/kg BW lactose PO and drawing glucose level at 0, 30, 45, 60, and 90 minutes. NI response is change in glucose from fasting value to >30 mg/dL. Inconclusive response is ↑ of 20 to 30 mg/dL; abnl response is ↑ <20 mg/dL.
Abnormal in: lactase deficiency.
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**LANOXIN; see DIGOXIN**

**LAP SCORE; see LEUKOCYTE ALKALINE PHOSPHATASE**

**LDH; see LACTATE DEHYDROGENASE**

**LDL; see LOW-DENSITY LIPOPROTEIN CHOLESTEROL**

**LEAD**

Normal: <10 μg/dL (child); <25 μg/dL (adult); <50 μg/dL (acceptable for industrial exposure).

Elevated in: lead exposure, lead poisoning.

**LEGIONELLA TITER**

Normal: negative.

Positive in: Legionnaire’s disease (presumptive, ≥1:256 titer; definitive, fourfold titer increase to ≥1:128).

**LEUKOCYTE ALKALINE PHOSPHATASE (LAP)**

Normal range: 13-100.

Elevated in: leukemoid reactions, neutrophilia resulting from infections (except in sickle cell crisis—no significant increase in LAP score), Hodgkin’s disease, PV, hairy cell leukemia, aplastic anemia, Down syndrome, myelofibrosis.

Decreased in: acute and chronic granulocytic leukemia, thrombocytopenic purpura, PNH, hypophosphatemia, collagen disorders.

**LH; see LUTEINIZING HORMONE**

**LIPASE**

Normal range: 0-160 U/L.

Elevated in: acute pancreatitis, perforated peptic ulcer, carcinoma of pancreas (early stage), pancreatic duct obstruction, bowel infarction, intestinal obstruction.

**LIPOPROTEIN(a)**

Normal: 1.35-19.6 mg/dL (male); 1.24-20.1 mg/dL (female).

Elevated in: CAD, uncontrolled diabetes, hypothyroidism, chronic renal failure, pregnancy, tobacco use, infections, nephritic syndrome.

Decreased in: niacin, omega-3 fatty acids, estrogens, tamoxifen.

**LIPOPROTEIN CHOLESTEROL, LOW DENSITY; see LOW-DENSITY LIPOPROTEIN CHOLESTEROL**

**LIPOPROTEIN CHOLESTEROL, HIGH DENSITY; see HIGH-DENSITY LIPOPROTEIN CHOLESTEROL**

**LIVER-KIDNEY MICROSONE TYPE 1 ANTIBODIES (LKM1)**

Normal: <20 U.

Elevated in: autoimmune hepatitis type 2.

**LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL**

Normal range: <130 mg/dL (<70 mg/dL in diabetics and pts w/CV risk factors).

Elevated in: diet high in saturated fat, familial hyperlipidemia, sedentary lifestyle, poorly controlled DM, nephritic syndrome, hypothyroidism.

Decreased in: use of lipid-lowering agents (statins, niacin, ezetimibe, cholestyramine, colesevelam), starvation, malabsorption, abetalipoproteinemia, hyperthyroidism, hepatic failure, carcinoma, infection, inflammation.

**LUPUS ANTICOAGULANT (LA) TEST**

Normal: negative.

Present in: antiphospholipid Ab syndrome. False-positive results may occur w/oral anticoagulant Rx, factor deficiency, specific factor inhibitors.
LUTEINIZING HORMONE (LH) (Blood)

Normal range:
- Female, adult: 1.0-18.0 IU/L (follicular phase); 20.0-80.0 IU/L (midcycle phase); 0.5-18.0 IU/L (luteal phase); postmenopausal: 12.0-55.0 IU/L
- Male, adult: 1.0-9.0 IU/L

Elevated in: gonadal failure, anorchia, menopause, testicular feminization syndrome.
Decreased in: primary pituitary or hypothalamic failure.

LYMPHOCYTES

Normal range: 15%-40%.
- Total lymphocyte count: 800-2600/mm³
- Total T lymphocytes: 800-2200/mm³
- CD4 lymphocytes: ≥400/mm³
- CD8 lymphocytes: 200-800/mm³
- Normal CD4/CD8 ratio is 2.0.

Elevated in: chronic infections, infectious mononucleosis and other viral infections, CLL, Hodgkin’s disease, UC, hypoadrenalism, ITP.
Decreased in: HIV infection, bone marrow suppression from chemotherapeutic agents or chemotherapy, aplastic anemia, neoplasms, steroids, adrenocortical hyperfunction, neurologic disorders (MS, myasthenia gravis, GBS).

CD4 lymphocytes are calculated as total WBCs × % lymphocytes × % lymphocytes stained w/CD4. They are decreased in AIDS and other forms of immune dysfunction.

MAGNESIUM (Serum)

Normal range: 1.8-3.0 mg/dL.
Abnormal: Refer to hypomagnesemia and hypermagnesemia in Section 3.

MEAN CORPUSCULAR VOLUME (MCV)

Normal range: 76-100 µm³.
Elevated in: EtOH abuse, reticulocytosis, vitamin B₁₂ deficiency, folic acid deficiency, liver disease, hypothyroidism, marrow aplasia, myelofibrosis.
Decreased in: Iron deficiency, anemia of chronic disease, thalassemia trait or syndrome, other hemoglobinopathies, sideroblastic anemia, chronic renal failure, lead poisoning.

METANEPHRINES, URINE; see URINE METANEPHRINES

METHYLMALONIC ACID (Serum)

Normal: <0.2 µmol/L.
Elevated in: vitamin B₁₂ deficiency, pregnancy, methylmalonic acidemia.

MITOCHONDRIAL ANTIBODY (AMA Antimitochondrial Antibody)

Normal: negative.
Present in: PBC (>90% of pts).

MONOCYTE COUNT

Normal range: 2%-8%.
Elevated in: viral diseases, parasites, infections, neoplasms, IBD, monocytic leukemia, lymphomas, myeloma, sarcoidosis.
Decreased in: viral syndrome, glucocorticoid administration, aplastic anemia, lymphocytic leukemia.

MYCOPLASMA PNEUMONIAE PCR

Test description: PCR can be performed on sputum, BAL fluid, nasopharyngeal and throat swabs, other respiratory fluids, and lung tissue.

MYELIN BASIC PROTEIN (Cerebrospinal Fluid)

Normal: <2.5 ng/mL.
Elevated in: MS, CNS trauma, stroke, encephalitis.
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MYOGLOBIN, URINE; see URINE MYOGLOBIN

NATRIURETIC PEPTIDE; see B-TYPE NATRIURETIC PEPTIDE

NEUTROPHIL COUNT

Normal range: 50%-70%.
Subsets:
- Bands (early mature neutrophils): 2%-6%
- Segs (mature neutrophils): 60%-70%

Decreased in: viral infections, aplastic anemias, immunosuppressive drugs, radiation Rx to bone marrow, agranulocytosis, drugs (abx, antithyroidals), lymphocytic and monocytic leukemias.

NOREPINEPHRINE

Normal range: 0-600 pg/mL.
Elevated in: pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla).

5’-NUCLEOTIDASE

Normal range: 2-16 IU/L.
Elevated in: biliary obstruction, metastatic neoplasms to liver, PBC, renal failure, pancreatic carcinoma, chronic active hepatitis.

OSMOLALITY, SERUM

Normal range: 280-300 mOsm/kg. It can also be estimated by the following formula: 2([Na] + [K]) + Glucose/18 + BUN/2.8.
Elevated in: dehydration, hypernatremia, diabetes insipidus, uremia, hyperglycemia, mannitol Rx, ingestion of toxins (ethylene glycol, methanol, ethanol), hypercalcemia, diuretics.
Decreased in: SIADH, hyponatremia, overhydration, Addison’s disease, hypothyroidism.

OSMOLALITY, URINE; see URINE OSMOLALITY

OSMOTIC FRAGILITY TEST

Normal: Hemolysis begins at 0.50, w/v [5.0 g/L] and is complete at 0.30, w/v [3.0 g/L] NaCl.
Elevated in: hereditary spherocytosis, hereditary stomatocytosis, spherocytosis associated w/acquired immune hemolytic anemia.
Decreased in: iron deficiency anemia, thalassemias, liver disease, leptocytosis associated w/asplenia.

PARATHYROID HORMONE

Normal: 10-65 pg/mL (serum, intact molecule); 1.0-5.0 pmol/L (plasma).
Elevated in: hyperparathyroidism (primary or secondary), pseudohypoparathyroidism, anticonvulsants, corticosteroids, lithium, isoniazid, rifampin, phosphates, Zollinger-Ellison syndrome, hereditary vitamin D deficiency.
Decreased in: hypoparathyroidism, sarcoidosis, cimetidine, beta-blockers, hyperthyroidism, hypomagnesemia.

PARIETAL CELL ANTIBODIES

Normal: negative.
Present in: pernicious anemia (>90%), atrophic gastritis (up to 50%), thyroiditis (30%), Addison’s disease, myasthenia gravis, Sjögren’s syndrome, type 1 DM.
PARTIAL THROMBOPLASTIN TIME (PTT), ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

Normal range: 25-41 seconds.

**Elevated in:** heparin Rx, coagulation factor deficiency (I, II, V, VIII, IX, X, XI, XII), liver disease, vitamin K deficiency, DIC, circulating anticoagulant, warfarin Rx, specific factor inhibition (PCN reaction, RA), thrombolytic Rx, nephrotic syndrome.

**Note:** useful to evaluate the intrinsic coagulation system.

PEPSINOGEN I

Normal: 124-142 ng/mL.

**Elevated in:** Zollinger-Ellison syndrome, duodenal ulcer, acute gastritis.

**Decreased in:** atrophic gastritis, gastric carcinoma, myxedema, pernicious anemia, Addison’s disease.

PFA: see PLATELET FUNCTION ANALYSIS (PFA-100 ASSAY)

pH, BLOOD

Normal values: 7.35-7.45 (arterial); 7.32-7.42 (venous).

**Abnormal values:** Refer to arterial blood gases.

pH, URINE; see URINE pH

PHOSPHATASE, ACID; see ACID PHOSPHATASE

PHOSPHATASE, ALKALINE; see ALKALINE PHOSPHATASE

PHOSPHATE (Serum)

Normal range: 2.5-5 mg/dL.

**Elevated in:** Refer to hyperphosphatemia and hypophosphatemia in Section 3.

PLASMINOGEN

Normal: Immunoassay (antigen), <20mg/dL.

**Elevated in:** infection, trauma, neoplasm, MI (acute-phase reactant), pregnancy, bilirubinemia.

**Decreased in:** DIC, severe liver disease, thrombolytic Rx w/streptokinase or urokinase, alteplase.

PLATELET AGGREGATION

Normal: full aggregation (generally >60%) in response to epinephrine, thrombin, ristocetin, ADP, collagen.

**Elevated in:** heparin, hemolysis, lipemia, nicotine; hereditary and acquired disorders of platelet adhesion, activation, and aggregation.

**Decreased in:** ASA, some PCNs, chloroquine, chlorpromazine, clofibrate, captopril, Glanzmann’s thrombasthenia, Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, cyclooxygenase deficiency. In vWD, there is nl aggregation w/ADP, collagen, and epinephrine but abnl agglutination w/ristocetin.

PLATELET ANTIBODIES

Normal: absent.

**Present in:** ITP (>90% of pts w/chronic ITP). Pts w/nonimmune thrombocytopenias may have false-positive results.

PLATELET COUNT

Normal range: 130-400 × 10^3/mm^3.

**Elevated in:** iron deficiency, post-hemorrhage, neoplasms (GI tract), CML, PV, myelofibrosis w/myeloid metaplasia, infections, after splenectomy, post partum, hemophilia, pancreatitis, cirrhosis.

**Decreased:** See thrombocytopenia in Section 3.
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PLATELET FUNCTION ANALYSIS (PFA-100 ASSAY)

Normal: This test is a two-component assay in which blood is aspirated through two capillary tubes, one of which is coated w/collagen and ADP (COL/ADP) and the other w/collagen and epinephrine (COL/EPI). The test measures the ability of platelets to occlude an aperture in a biologically active membrane treated with COL/ADP and COL/EPI. During the test, the platelets adhere to the surface of the tube and cause blood flow to cease. The closing time refers to the cessation of blood flow and is reported in conjunction w/the Hct and platelet count. Hct count must be >25% and platelet count >50 K/µL for the test to be performed.
- COL/ADP: 70-120 seconds
- COL/EPI: 75-120 seconds
Elevated in: acquired platelet dysfunction, vWD, anemia, thrombocytopenia, use of ASA and NSAIDs.

POTASSIUM (Serum)
Normal range: 3.5-5 mEq/L.
Elevated or decreased: See hypokalemia and hyperkalemia in Section 3.

POTASSIUM, URINE; see URINE POTASSIUM

PROGESTERONE (Serum)
Normal:
- Female: 15-70 ng/dL (follicular phase); 200-2500 ng/dL (luteal phase)
- Male: 15-70 ng/dL
Elevated in: congenital adrenal hyperplasia, clomiphene, corticosterone, 11-deoxycortisol, dihydropregesterone, molar pregnancy, lipid ovarian tumor.
Decreased in: primary or secondary hypogonadism, oral contraceptives, ampicillin, threatened abortion.

PROLACTIN
Normal range: <20 ng/mL.
Elevated in: prolactinomas (level >200 highly suggestive), drugs (phenothiazines, cimetidine, tricyclic antidepressants, metoclopramide, estrogens, anti hypertensives [methylidopa, verapamil], haloperidol), post partum, stress, hypoglycemia, hypothyroidism.

PROSTATE-SPECIFIC ANTIGEN (PSA)
Normal range: 0-4 ng/mL. There is no PSA level below which prostate cancer can be ruled out and no level above which prostate cancer is certain. The individual’s PSA level is only part of the equation. Other risk factors need to be considered, such as age, race, FHx, findings on digital rectal examination, percentage free PSA ratio, and PSA velocity (rate of change from prior PSA measurement).
Note: Measurement of free PSA is useful to assess the probability of prostate cancer in pts w/nl findings on digital rectal examination and total PSA level between 4 and 10 ng/mL. In these pts, the global risk of prostate cancer is 25% to 40%. However, if the free PSA is >25%, the risk of prostate cancer decreases to 8%; whereas if the free PSA is <10%, the risk of cancer increases to 56%. Free PSA is also useful to evaluate the aggressiveness of prostate cancer. A low free PSA percentage generally indicates a high-grade cancer, whereas a high free PSA percentage is generally associated w/a slower growing tumor.
Elevated in: finasteride, dutasteride, bed rest, antiandrogens.

PROSTATIC ACID PHOSPHATASE
Normal: 0-0.8 U/L.
Elevated in: prostate cancer (especially in metastatic prostate cancer), BPH, prostatitis, after prostate surgery or manipulation, hemolysis, androgens, clofibrate.
Decreased in: ketoconazole Rx.
Chapter 1  Surviving the Wards

PROTEIN (Serum)

**Normal range:** 6-8 g/dL.

**Elevated in:** dehydration, sarcoidosis, collagen-vascular diseases, MM, Waldenström’s macroglobulinemia.

**Decreased in:** malnutrition, cirrhosis, nephrosis, low-protein diet, overhydration, malabsorption, pregnancy, severe burns, neoplasms, chronic diseases.

**PROTEIN C ASSAY**

**Normal:** 70%-140%.

**Elevated in:** oral contraceptives, stanozolol.

**Decreased in:** congenital protein C deficiency, warfarin Rx, vitamin K deficiency, renal insufficiency, consumptive coagulopathies.

**PROTEIN ELECTROPHORESIS (Serum)**

**Normal range:**
- Alb: 60%-75%; 3.6-5.2 g/dL
- Alpha1: 1.7%-5%; 0.1-0.4 g/dL
- Alpha2: 6.7%-12.5%; 0.4-1.0 g/dL
- Beta: 8.3%-16.3%; 0.5-1.2 g/dL
- Gamma: 10.7%-20%; 0.6-1.6 g/dL

**Elevated in:**
- Alb: dehydration
- Alpha1: neoplastic diseases, inflammation
- Alpha2: neoplasms, inflammation, infection, nephrotic syndrome
- Beta: hypothyroidism, biliary cirrhosis, DM
- Gamma: see immunoglobulins

**Decreased in:**
- Alb: malnutrition, chronic liver disease, malabsorption, nephrotic syndrome, burns, SLE
- Alpha1: emphysema (alpha1-antitrypsin deficiency), nephrosis
- Alpha2: hemolytic anemias (decreased haptoglobin), severe hepatocellular damage
- Beta: hypocholesterolemia, nephrosis
- Gamma: see immunoglobulins

**PROTEIN S ASSAY**

**Normal:** 65%-140%.

**Elevated in:** presence of lupus anticoagulant.

**Decreased in:** hereditary deficiency, acute thrombotic events, DIC, surgery, oral contraceptives, pregnancy, hormone replacement Rx, L-asparaginase treatment.

**PROTHROMBIN TIME (PT)**

**Normal range:** 11-13.2 seconds.

**Note:** The PT is reported as absolute clotting time in seconds and also as a derivative number called the INR. This ratio is derived from the actual PT of the patient divided by the mean PT of a group of healthy subjects. INR should always be used in interpreting PT.

**Elevated in:** liver disease, oral anticoagulants (warfarin), heparin, factor deficiency (I, II, V, VII, X), DIC, vitamin K deficiency, afibrinogenemia, dysfibrinogenemia, drugs (salicylate, chloral hydrate, diphenyldantoin, estrogens, antacids, phenylbutazone, quinidine, abx, allopurinol, anabolic steroids).

**Decreased in:** vitamin K supplementation, thrombophlebitis, drugs (glutethimide, estrogens, griseofulvin, diphenhydramine).

**PROTOPORPHYRYIN (Free Erythrocyte)**

**Normal range:** 16-36 µg/dL of RBCs.

**Elevated in:** iron deficiency, lead poisoning, sideroblastic anemias, anemia of chronic disease, hemolytic anemias, erythropoietic protoporphyria.
PSA; see PROSTATE-SPECIFIC ANTIGEN
PT; see PROTHROMBIN TIME
PTT; see PARTIAL THROMBOPLASTIN TIME
RDW; see RED BLOOD CELL DISTRIBUTION WIDTH

RED BLOOD CELL COUNT
Normal range: 4.3–5.9 × 10^6/mm³ (male); 3.5–5.0 × 10^6/mm³ (female).
Elevated in: hemoconcentration and dehydration, stress, PV, smokers, high altitude, CV disease, renal cell carcinoma and other erythropoietin-producing neoplasms.
Decreased in: anemias, hemolysis, chronic renal failure, hemorrhage, failure of marrow production.

RED BLOOD CELL DISTRIBUTION WIDTH (RDW)
RDW measures variability of red cell size (anisocytosis).
Normal range: 11.5–14.5.
Normal RDW and:
- Elevated MCV: aplastic anemia, preleukemia.
- Normal MCV: normal, anemia of chronic disease, acute blood loss or hemolysis, CLL, CML, non-anemic enzymopathy or hemoglobinopathy.
- Decreased MCV: anemia of chronic disease, heterozygous thalassemia.

Elevated RDW and:
- Elevated MCV: vitamin B₁₂ deficiency, folate deficiency, immune hemolytic anemia, cold agglutinins, CLL w/high count, liver disease.
- Normal MCV: early iron deficiency, early vitamin B₁₂ deficiency, early folate deficiency, anemic globinopathy.
- Decreased MCV: iron deficiency, RBC fragmentation, HbH disease, thalassemia intermedia.

RED BLOOD CELL FOLATE; see FOLATE

RED BLOOD CELL MASS (Volume)
Normal range:
- Male: 20–56 mL/kg of BW (1.15-1.21 L/m² BSA)
- Female: 19–31 mL/kg of BW (0.95-1.00 L/m² BSA)
Elevated in: P vera, hypoxia (smokers, high altitude, CV disease), hemoglobinopathies w/high oxygen affinity, erythropoietin-producing tumors (renal cell carcinoma).
Decreased in: hemorrhage, chronic disease, failure of marrow production, anemias, hemolysis.

RENIN (Serum)
Elevated in: renal HTN, reduced plasma volume, secondary aldosteronism, drugs (thiazides, estrogen, minoxidil), chronic renal failure, Bartter’s syndrome, pregnancy (nl), pheochromocytoma.
Decreased in: primary aldosteronism, adrenocortical HTN, increased plasma volume, drugs (propranolol, reserpine, clonidine).

RETICULOCYTE COUNT
Normal range: 0.5%–1.5%.
Elevated in: hemolytic anemia (sickle cell crisis, thalassemia major, autoimmune hemolysis), hemorrhage, post–anemia Rx (folic acid, ferrous sulfate, vitamin B₁₂), chronic renal failure.
Decreased in: aplastic anemia, marrow suppression (sepsis, chemotherapeutic agents, radiation), hepatic cirrhosis, blood transfusion, anemias of disordered maturation (iron deficiency anemia, megaloblastic anemia, sideroblastic anemia, anemia of chronic disease).
RHEUMATOID FACTOR (RF)
Normal: negative.

RNP; see EXTRACTABLE NUCLEAR ANTIGEN

SEDIMENTATION RATE; see ERYTHROCYTE SEDIMENTATION RATE

SEMEN ANALYSIS
Normal:
- Volume: 2-6 mL
- Sperm density: >20 million/mL
- Total number of spermatozoa: >80 million/ejaculate
- Progressive motility score evaluated 2-4 hours after ejaculate: 3-4
- Live spermatozoa: ≥50% of total
- Normal spermatozoa: ≥60% of total
- Immature forms: <4%
Decreased in: cryptorchidism, testicular failure, obstruction of ejaculatory system, post-vasectomy, medications (cimetidine, ketoconazole, nitrofurantoin, cancer chemotherapy agents, sulfasalazine), testicular radiation.

SGOT; see ASPARTATE AMINOTRANSFERASE
SGPT; see ALANINE AMINOTRANSFERASE

SICKLE CELL TEST
Normal: negative.
Positive in: sickle cell anemia, sickle cell trait; combination of Hgb S gene w/other disorders, such as α-thalassemia, β-thalassemia.

SMOOTH MUSCLE ANTIBODY
Normal: negative.
Present in: chronic active hepatitis (≥1:80), PBC (≥1:80), infectious mononucleosis.

SODIUM (Serum)
Normal range: 135-147 mEq/L.
Elevated or decreased: See hyponatremia and hypernatremia in Section 3.

STREPTOZYME; see ANTISTREPTOLYSIN O TITER

SUDAN III STAIN (Qualitative Screening for Fecal Fat)
Normal: negative. The test should be preceded by a diet containing 100 to 150 g of dietary fat/day for 1 week, avoidance of high-fiber diet, and avoidance of suppositories or oily material before specimen collection.
Positive in: steatorrhea, use of castor oil or mineral oil droplets.

T₃ (TRIIODOOTHYRONINE)
Normal range: 75-220 ng/dL.
Abnormal values: See hypothyroidism and hyperthyroidism in Section 3.

T₃ RESIN UPTAKE (T₃RU)
Normal range: 25%-35%.
Abnormal values: ↑ in hyperthyroidism. T₃ resin uptake (T₃RU or RT₃U) measures the percentage of free T₃ (not bound to protein); it does not measure serum T₃ concentration. T₃RU and other tests that reflect thyroid hormone binding to plasma protein are also known as thyroid hormone–binding ratios (THBR).
**T₄, SERUM T₄, AND FREE T₄ (Free Thyroxine)**

**Normal range:** 0.8-2.8 ng/dL.

**Abnormal values:** See hyperthyroidism in Section 3. Serum thyroxine test measures both circulating thyroxine bound to protein (represents >99% of circulating T₄) and unbound [free] thyroxine. Values vary w/protein binding; changes in the concentration of T₄ secondary to changes in thyroxine-binding globulin (TBG) can be caused by the following:

- Increased TBG (↑ T₄): pregnancy, estrogens, acute infectious hepatitis, oral contraceptives, familial, fluorouracil, clofibrate, heroin, methadone.
- Decreased TBG (↓ T₄): androgens, glucocorticoids, nephrotic syndrome, cirrhosis, acromegaly, hypoproteinemia, familial, phenytoin, ASA and other NSAIDs, high-dose PCN, aspirin, chronic debilitating illness.

To eliminate the suspected influence of protein binding on thyroxine values, two additional tests are available: T₃ resin uptake and serum free thyroxine. Serum free T₄ directly measures unbound thyroxine. Free T₄ can be measured by equilibrium dialysis (gold standard of free T₄ assays) or by immunometric techniques (influenced by serum levels of lipids, proteins, and certain drugs).

The FTI can also be easily calculated by multiplying T₄ times T₃RU and dividing the result by 100; the FTI corrects for any abnl T₄ values secondary to protein binding: FTI = T₄ × T₃RU/100. NI values equal 1.1 to 4.3.

**TESTOSTERONE**

**Normal range:** variable with age and sex.
- Serum/plasma: 280-1000 ng/dL (males); 15-70 ng/dL (females)
- Urine: 50-135 µg/day (males); 2-12 µg/day (females)

**Elevated in:** adrenogenital syndrome, polycystic ovary disease.

**Decreased in:** Klinefelter’s syndrome, male hypogonadism.

**THIAMINE**

**Normal:** 275-675 ng/g.

**Elevated in:** PV, leukemia, Hodgkin’s disease.

**Decreased in:** alcoholism, dietary deficiency (beri-beri), excessive consumption of tea (contains antithiamine factor) or raw fish (contains a microbial thiaminase), chronic illness, prolonged illness, barbiturates.

**THROMBIN TIME (TT)**

**Normal range:** 11.3-18.5 seconds.

**Elevated in:** thrombolytic and heparin Rx, DIC, hypofibrinogenemia, dysfibrinogenemia.

**THYROGLOBULIN**

**Normal:** 3-40 ng/mL. Thyroglobulin is a tumor marker for monitoring the status of pts w/papillary or follicular thyroid cancer after resection.

**Elevated in:** papillary or follicular thyroid cancer, Hashimoto’s thyroiditis, Graves’ disease, subacute thyroiditis.

**THYROID MICROSOMAL ANTIBODIES**

**Normal:** undetectable. Low titers may be present in 5% to 10% of nl individuals.

**Elevated in:** Hashimoto’s disease, thyroid carcinoma, early hypothyroidism, pernicious anemia.

**THYROID-STIMULATING HORMONE (TSH)**

**Normal range:** 2-11.0 µU/mL.

**Elevated:** See hypothyroidism in Section 3.

**THYROTROPIN (TSH) RECEPTOR ANTIBODIES**

**Normal:** <130% of basal activity.

**Elevated in:** Values between 1.3 and 2.0 are found in 10% of pts w/Graves’ disease other than Graves’ disease. Values >2.8 have been found only in pts w/Graves’ disease.
TIBC; see IRON-BINDING CAPACITY

TISSUE TRANSGlutAmINASE ANtiBody

Normal: negative.
Present in: celiac disease (specificity, 94%-97%; sensitivity, 90%-98%), dermatitis herpetiformis.

TRANSFERRIN

Normal range: 170-370 mg/dL.
Elevated in: iron deficiency anemia, oral contraceptive administration, viral hepatitis, late pregnancy.
Decreased in: nephrotic syndrome, liver disease, hereditary deficiency, protein malnutrition, neoplasms, chronic inflammatory states, chronic illness, thalassemia, hemochromatosis, hemolytic anemia.

TRIGlycerides

Normal range: <160 mg/dL.
Elevated in: hyperlipoproteinemias (types I, IIb, III, IV, V), diet high in saturated fats, hypothyroidism, pregnancy, estrogens, pancreatitis, EtOH intake, nephrotic syndrome, poorly controlled DM, sedentary lifestyle, glycogen storage disease.
Decreased in: malnutrition, vigorous exercise, congenital abetalipoproteinemias, drugs (e.g., gemfibrozil, fenofibrate, nicotinic acid, metformin, clofibrate).

TRIIODOTHYRONINE; see T₃

TROpONINs (Serum)

Normal range: 0-0.4 ng/mL (negative). If there is clinical suspicion of evolving acute MI or ischemic episode, repeated testing in 5 to 6 hours is recommended.
Indeterminate: 0.05-0.49 ng/mL. Suggest further tests. In a patient w/unstable angina and this troponin I level, there is an increased risk of a cardiac event in the near future.
Strong probability of acute MI: ≥0.50 ng/mL.
- Cardiac troponin T (cTnT) is a highly sensitive marker for myocardial injury for the first 48 hours after MI and for up to 5 to 7 days. It may also be elevated in renal failure, chronic muscle disease, and trauma.
- Cardiac troponin I (cTnl) is highly sensitive and specific for myocardial injury (≥CK-MB) in the initial 8 hours, peaks within 24 hours, and lasts up to 7 days. With progressively higher levels of cTnl, the risk of mortality increases because the amount of necrosis increases.
Elevated in: In addition to ACS, many diseases such as sepsis, hypovolemia, AF, CHF, PE, myocardial contusion, and renal failure can be associated w/↑ in troponin level.

TSH; see THyroid-stimuLATING Hormone

TT; see THromBIN TIME

UNCONjUGATED BILIRUBIN; see BILIRUBIN, INDIRECT

UREA NITROGEN

Normal range: 8-18 mg/dL.
Elevated in: dehydration, renal disease (GN, pyelonephritis, diabetic nephropathy), urinary tract obstruction (prostatic hypertrophy), drugs (AGs and other abx, diuretics, lithium, corticosteroids), Gl bleeding, decreased renal blood flow (shock, CHF, MI).
Decreased in: liver disease, malnutrition, third trimester of pregnancy.

URIC ACID (Serum)

Normal range: 2-7 mg/dL.
Elevated in: hereditary enzyme deficiency (hypoxanthine-guanine phosphoribosyltransferase), renal failure, gout, excessive cell lysis
(chemotherapeutic agents, radiation Rx, leukemia, lymphoma, hemolytic anemia), acidosis, myeloproliferative disorders, diet high in purines or protein, drugs (diuretics, low doses of ASA, ethambutol, nicotinic acid), lead poisoning, hypothyroidism.

**Decreased in:** drugs (allopurinol, high doses of ASA, probenecid, warfarin, corticosteroid), deficiency of xanthine oxidase, SIADH, renal tubular deficits (Fanconi’s syndrome), alcoholism, liver disease, diet deficient in protein or purines, Wilson’s disease, hemochromatosis.

**URINALYSIS**

**Normal range:**
- Color: light straw
- Appearance: clear
- pH: 4.5-8.0 (average, 6.0)
- Specific gravity: 1.005-1.030
- Protein: absent
- Ketones: absent
- Glucose: absent
- Occult blood: absent
- Microscopic examination:
  - RBC: 0-5 (high-power field)
  - WBC: 0-5 (high-power field)
  - Bacteria (spun specimen): absent
  - Casts: 0-4 hyaline (low-power field)

**URINE AMYLASE**

**Normal range:** 35-260 U Somogyi/hr.

**Elevated in:** pancreatitis, carcinoma of the pancreas.

**URINE BILE**

**Normal:** absent.

**Abnormal:**
- Urine bilirubin: hepatitis (viral, toxic, drug induced), biliary obstruction.
- Urine urobilinogen: hepatitis (viral, toxic, drug induced), hemolytic jaundice, liver cell dysfunction (cirrhosis, infection, mets).

**URINE CALCIUM**

**Normal:** 6.2 mmol/dL (CF, 0.02495; SMI, 0.1 mmol/dL).

**Elevated in:** primary hyperparathyroidism, hypervitaminosis D, bone mets, MM, increased Ca intake, steroids, prolonged immobilization, sarcoidosis, Paget’s disease, idiopathic hypercalciuria, renal tubular acidosis.

**Decreased in:** hypoparathyroidism, pseudohypoparathyroidism, vitamin D deficiency, vitamin D-resistant rickets, diet low in Ca, drugs (thiazide diuretics, oral contraceptives), familial hypocalciuric hypercalcemia, renal osteodystrophy, potassium citrate Rx.

**URINE cAMP**

**Elevated in:** hypercalciuria, familial hypocalciuric hypercalcemia, primary hyperparathyroidism, pseudohypoparathyroidism, rickets.

**Decreased in:** vitamin D intoxication, sarcoidosis.

**URINE CATECHOLAMINES**

**Normal range:** <100 µg/24 hr (norepinephrine); <10 µg/24 hr (epinephrine).

**Elevated in:** pheochromocytoma, neuroblastoma, severe stress.

**URINE CHLORIDE**

**Normal range:** 110-250 mEq/day.

**Elevated in:** corticosteroids, Bartter’s syndrome, diuretics, metabolic acidosis, severe hypokalemia.

**Decreased in:** chloride depletion (vomiting), colonic villous adenoma, chronic renal failure, renal tubular acidosis.
URINE CREATININE (24-Hour)
Normal range: 0.8-1.8 g/day (male); 0.6-1.6 g/day (female).
Note: useful test as an indicator of completeness of 24-hour urine collection.

URINE CRYSTALS
Uric acid: acid urine, hyperuricosuria, uric acid nephropathy.
Sulfur: abx containing sulfa.
Calcium oxalate: ethylene glycol poisoning, acid urine, hyperoxaluria.
Calcium phosphate: alkaline urine.
Cystine: cystinuria.

URINE EOSINOPHILS
Normal: absent.
Present in: interstitial nephritis, ATN, UTI, kidney transplant rejection, HRS.

URINE GLUCOSE (QUALITATIVE)
Normal: absent.
Present in: DM, renal glycosuria (decreased renal threshold for glucose), glucose intolerance.

URINE HEMOGLOBIN, FREE
Normal: absent.
Present in: hemolysis (w/saturation of serum haptoglobin binding capacity and renal threshold for tubular absorption of Hgb).

URINE HEMOSIDERIN
Normal: absent.
Present in: PNH, chronic hemolytic anemia, hemochromatosis, blood transfusion, thalassemias.

URINE 5-HYDROXYINDOLEACETIC ACID (URINE 5-HIAA)
Normal range: 2-8 mg/24 hr.
Elevated in: carcinoid tumors, after ingestion of certain foods (bananas, plums, tomatoes, avocados, pineapples, eggplant, walnuts), drugs (MAOIs, phenacetin, methylpoda, glycerol guaiacolate, acetaminophen, salicylates, phenothiazines, imipramine, methocarbamol, reserpine, methamphetamine).

URINE INDICAN
Normal: absent.
Present in: malabsorption resulting from intestinal bacterial overgrowth.

URINE KETONES (Semiquantitative)
Normal: absent.
Present in: DKA, alcoholic ketoacidosis, starvation, isopropanol ingestion.

URINE METANEPHRINES
Normal range: 0-2.0 mg/24 hr.
Elevated in: pheochromocytoma, neuroblastoma, drugs (caffeine, phenothiazines, MAOIs), stress.

URINE MYOGLOBIN
Normal: absent.
Present in: severe trauma, hyperthermia, polymyositis or dermatomyositis, CO poisoning, drugs (narcotic and amphetamine toxicity), hypothyroidism, muscle ischemia.

URINE NITRITE
Normal: absent.
Present in: UTIs.
URINE OCCULT BLOOD
Normal: negative.
Positive in: trauma to urinary tract, renal disease (GN, pyelonephritis),
renal or ureteral calculi, bladder lesions (carcinoma, cystitis), prostatitis,
prostatic carcinoma, menstrual contamination, hematopoietic disorders
(hemophilia, thrombocytopenia), anticoagulants, ASA.
Note: Hematuria w/o erythrocyte casts or significant albuminuria suggests
the possibility of renal or bladder cancers.

URINE OSMOLALITY
Normal range: 50-1200 mOsm/kg.
Elevated in: SIADH, dehydration, glycosuria, adrenal insufficiency,
high-protein diet.
Decreased in: diabetes insipidus, excessive water intake, IV hydration
w/D3W, acute renal insufficiency, GN.

URINE pH
Normal range: 4.6-8.0 (average 6.0).
Elevated in: bacteriuria, vegetarian diet, renal failure w/inability to form
ammonia, drugs (abx, sodium bicarbonate, acetazolamide).
Decreased in: acidosis (metabolic, respiratory), drugs (ammonium chloride,
methenamine mandelate), DM, starvation, diarrhea.

URINE PHOSPHATE
Normal range: 0.8-2.0 g/24 hr.
Elevated in: ATN (diuretic phase), chronic renal disease, uncontrolled DM,
hyperparathyroidism, hypomagnesemia, metabolic acidosis, metabolic
alkalosis, neurofibromatosis, adult-onset vitamin D–resistant
hypophosphatemic osteomalacia.
Decreased in: acromegaly, ARF, decreased dietary intake,
hypoparathyroidism, respiratory acidosis.

URINE POTASSIUM
Normal range: 25-100 mEq/24 hr.
Elevated in: aldosteronism (primary, secondary), glucocorticoids, alkalosis,
renal tubular acidosis, excessive dietary K+ intake.
Decreased in: ARF, potassium-sparring diuretics, diarrhea, hypokalemia.

URINE PROTEIN (Quantitative)
Normal range: <150 mg/24 hr.
Elevated in: renal disease (glomerular, tubular, interstitial), CHF, HTN,
neoplasms of renal pelvis and bladder, MM, Waldenström’s
macroglobulinemia.

URINE SODIUM (Quantitative)
Normal range: 40-220 mEq/day.
Elevated in: diuretic administration, high sodium intake, salt-losing
nephritis, ATN, vomiting, Addison’s disease, SIADH, hypothyroidism, CHF,
hepatic failure, chronic renal failure, Bartter’s syndrome, glucocorticoid
deficiency, interstitial nephritis (caused by analgesic abuse, mannitol,
dextran, or glycerol Rx), milk-alkali syndrome, decreased renin secretion,
postobstructive diuresis.
Decreased in: increased aldosterone, glucocorticoid excess, hyponatremia,
prerenal azotemia, decreased salt intake.

URINE SPECIFIC GRAVITY
Normal range: 1.005-1.03.
Elevated in: dehydration, excessive fluid losses (vomiting, diarrhea, fever),
-x-ray contrast media, DM, CHF, SIADH, adrenal insufficiency, decreased
fluid intake.
Decreased in: diabetes insipidus, renal disease (GN, pyelonephritis),
excessive fluid intake or IV hydration.
URINE VANILLYLMANDELIC ACID (VMA)

Normal range: <6.8 mg/24 hr.
Elevated in: pheochromocytoma, neuroblastoma, ganglioblastoma, drugs (isoproterenol, methocarbamol, levodopa, sulfonamides, chlorpromazine), severe stress; after ingestion of bananas, chocolate, vanilla, tea, coffee.
Decreased in: drugs (MAOIs, reserpine, guanethidine, methylprednisolone).

VASSOCATIVE INTESTINAL PEPTIDE (VIP)

Normal: <50 pg/mL.
Elevated in: pancreatic VIPomas, neuroblastoma, pancreatic islet cell hyperplasia, liver disease, multiple endocrine neoplasia type I, ganglioneuroma, ganglioneuroblastoma.

VENEREAL DISEASE RESEARCH LABORATORIES (VDRL)

Normal: Negative.
Positive test: syphilis, other treponemal diseases (yaws, pinta, bejel).
Note: A false-positive test result may be seen in pts w/SLE and other autoimmune diseases, infectious mononucleosis, HIV infection, atypical pneumonia, malaria, leprosy, typhus fever, rat-bite fever, and relapsing fever.

VIP; see VASSOCATIVE INTESTINAL PEPTIDE

VISCOSITY (Serum)

Normal range: 1.4-1.8 relative to water (1.10-1.22 centipoise).
Elevated in: monoclonal gammapathies (Waldenström’s macroglobulinemia, MM), hyperfibrinogenemia, SLE, RA, polycythemia, leukemia.

VITAMIN B_{12}

Normal range: 190-900 ng/mL.
Decreased in: pernicious anemia, dietary (strict lacto-ovo-vegetarians, food faddists), malabsorption (achlorhydria, gastrectomy, ileal resection, Crohn’s disease of terminal ileum, pancreatic insufficiency, drugs [omeprazole and other PPIs, metformin, cholestyramine]), chronic alcoholism, Helicobacter pylori infection.

VITAMIN D, 1,25-DIHYDROXYCHOLECALCIFEROL

Normal: 16-65 pg/mL.
Elevated in: tumor calcinosis, primary hyperparathyroidism, sarcoidosis, tuberculosis, idiopathic hypercalciuria.
Decreased in: Postmenopausal osteoporosis, chronic renal failure, hypoparathyroidism, tumor-induced osteomalacia, rickets, elevated blood lead levels.

VITAMIN K

Normal: 0.10-2.20 ng/mL.
Decreased in: PBC, anticoagulants, abx, cholestyramine, GI disease, pancreatic disease, cystic fibrosis, obstructive jaundice, hypoprothrombinemia, hemorrhagic disease of the newborn.

VON WILLEBRAND FACTOR

Normal: levels vary according to blood type: 50-150 U/dL (blood type O); 90-200 U/dL (blood type non-O).
Decreased in: vWD (however, in type II vWD, the antigen may be nl but the function is impaired).

WBCS; see COMPLETE BLOOD COUNT

WESTGREN; see ERYTHROCYTE SEDIMENTATION RATE

WHITE BLOOD CELL COUNT; see COMPLETE BLOOD COUNT

D-XYLOSE ABSORPTION

Normal range: 21%-31% excreted in 5 hours.
Decreased in: malabsorption syndrome.
D. Diagnostic Tests: The Basics

1. THE CHEST X-RAY

Figure 1-7 illustrates the location of various pulmonary and cardiac structures seen on a CXR (PA view). The following is a short guide to reading a CXR.

1. Check exposure technique for lightness or darkness.
2. Verify left and right by looking at the heart shape and stomach bubble, respectively.
3. Check for rotation. Does the thoracic spine shadow align in the center of the sternum between the clavicles?
4. Make sure the x-ray is taken in full inspiration (10 posterior or 6 anterior ribs should be visible).
5. Is the film a portable, AP, or PA film? (The heart size cannot be accurately judged from an AP film.)
6. Check the soft tissues for foreign bodies or SC emphysema.
7. Check all visible bones and joints for osteoporosis, old fxs, metastatic lesions, rib notching, or presence of cervical ribs.
8. Look at diaphragm for tenting, free air, and position.
9. Check hilar and mediastinal areas for the following: size and shape of aorta, presence of hilar nodes, prominence of hilar blood vessels, elevation of vessels (left normally slightly higher), elevation of left main stem bronchus indicating left atrial enlargement.
10. Look at heart for size, shape, calcified valves, and enlarged atria.
11. Check costophrenic angles for fluid or pleural scarring.
12. Check pulmonary parenchyma for infiltrates, increased interstitial markings, masses, absence of nl margins, air bronchograms, or increased vascularity and “silhouette” signs.
13. Look at lateral film for the following: confirmation and position of questionable masses or infiltrates, size of retrosternal air space, AP chest diameter, vertebral bodies for bony lesions or overlying infiltrates, posterior costophrenic angle for small effusion.

2. THE ELECTROCARDIOGRAM

1. Determine the heart rate (HR). If the heart rhythm is regular, the HR can be determined by dividing 300 by the number of boxes in the R-R interval (e.g., if R-R interval contains four large boxes, the HR is 75 bpm.
The HR can also be calculated by use of the following formula: each large square = 0.2 sec; 5 large squares/sec. For specific rate, measure large squares between R waves as follows:

- a. 1 = 300 bpm
- b. 2 = 150 bpm
- c. 3 = 100 bpm
- d. 4 = 75 bpm
- e. 5 = 60 bpm
- f. 6 = 50 bpm

2. Determine the heart rhythm.
   a. Is the rhythm regular?
   b. Are there P waves (Fig. 1-8)?
   c. Is the P wave related to the QRS (i.e., are P waves “married” to the QRS)?
   d. The P wave should always be upright in lead II if there is sinus rhythm (unless there is reversal of leads or dextrocardia). If the rhythm is irregular, the P wave can help w/the dx (e.g., w/sinus arrhythmia, the P waves will be identical; w/wandering pacemaker, the P waves will have different shapes; w/AF, the P waves are not discernible).
3. Evaluate the intervals.
   a. **PR interval**: nl is 0.12 to 0.20 sec (for practical purposes, the PR interval is nl if it does not exceed a large box). The PR interval becomes shorter as the rate increases.
   b. **QRS interval** (Fig. 1-9): nl is 0.04 to 0.12 sec (for practical purposes, the QRS interval should not be > half a large box). If the QRS is wide, evaluate for BBB.
      i. **LBBB**: The following may be seen:
         (a) Wide slurred R in V5-6.
         (b) QRS prolonged ≥0.12 sec, lengthened VAT or intrinsiocid deflection.
         (c) AVL similar to V5-6, lead I similar to aVL and V5-6 (w/depression of the ST segments and inversion of the T waves).
ii. **RBBB:**
   (a) QRS ≥0.12 sec.
   (b) Wide slurred S waves in V_{5-6}, rsR' complexes in V_{3R} and V_{1,2}, w-absent Q waves.
   (c) VAT prolonged in V_{3R} and V_{1,2}; a wide S wave in lead I.

   **c. QT interval:** the nl QT interval should be < half the R-R interval (if the HR is <100 bpm). Normal is ≤440 msec.

4. Determine the **axis deviation:** look at the net QRS deflection in leads I and aVF.
   a. Normal axis: net QRS deflection is positive in both leads I and aVF.
   b. RAD: net QRS deflection negative in lead I, positive in lead aVF.
   c. LAD: net QRS deflection positive in lead I, negative in lead aVF.
   d. Indeterminate axis: net QRS deflection negative in leads I and aVF.

5. **Hypertrophy:** look for signs of enlargement of the four chambers.
   a. LVH: the sum of the deepest S in V_{1} or V_{2} and the tallest R in V_{5} or V_{6} is >35 mm (in pts ≥35 years of age); R in lead aVL ≥12 mm; “strain” pattern.
   b. Left atrial hypertrophy (P mitrale): the P waves are notched (M shaped) in the mitral leads (I, II, or aVL), or there is a deep terminal negative component to the P in lead V_{1}.
   c. Right atrial hypertrophy (P pulmonale): the P waves are prominent (≥2.5 mm tall) and peaked in the pulmonary leads (II, III, and aVF).
   d. RVH: findings suggestive of RVH in adults are right atrial enlargement, RAD, incomplete RBBB, low voltage, tall R wave in V_{1}, persistent precordial S waves, right ventricular strain.

6. **Infarct:** look at all leads (except aVR) for:
   a. Q waves: small (nl septal Q waves) are commonly seen in lateral leads (I, aVL, V_{a}, V_{5}, and V_{6}); moderate- or large-sized Q waves may be nl (as an isolated finding) in leads III, aVF, aVL, and V_{1}.
   b. R-wave progression: transition should occur between V_{2} and V_{4}.
   c. ST segments: concentrate more on shape (i.e., “smiley” or “frowny”) than on the amount of ST-segment deviation.
   d. T waves: may normally be inverted in leads III, aVF, aVL, and V_{1}.

# THE PULMONARY ARTERY CATHETER (SWAN-GANZ)

1. **Figure 1-10** describes pressure waves.
2. **Table 1-11** describes hemodynamic measurements and their clinical significance.

**Figure 1-10.** A Swan-Ganz catheter is introduced into a large vein and advanced in the direction of blood flow. Vena cava pressure and RAP are about 0 to 5 mm Hg. Right ventricular pressure is 25/0 mm Hg; pulmonary artery pressure is 25/15 mm Hg. Inflation of the balloon on the catheter allows recording of the PAWP, about 8 mm Hg, which is a good estimate of pulmonary venous BP.
<table>
<thead>
<tr>
<th>Hemodynamic Measurement</th>
<th>Normal Value</th>
<th>Clinical Significance</th>
<th>Abnormalities</th>
</tr>
</thead>
</table>
| Right atrial pressure (RAP) | 0-8 mm Hg | Equivalent to CVP | ↑: Right ventricular failure, PE, tricuspid valve abnormalities, pericardial tamponade, right ventricular infarction  
↓: Hypovolemia |
| Pulmonary artery pressure (PAP) | Systolic: 15-30 mm Hg  
Diastolic: 5-12 mm Hg  
Mean: 10-20 mm Hg | PAP is equal to RAP during systole while the pulmonary valve is open  
If the pulmonary vascular resistance is normal, the PADP is 1-4 mm Hg > PCWP and can be substituted for it in following the patient’s hemodynamic measurements | ↑: PE, chronic lung disease, VSD, cardiogenic shock, right ventricular infarction  
↓: Hypovolemia |
| Pulmonary capillary wedge pressure (PCWP) | 5-12 mm Hg | PCWP is normally equal to left atrial pressure; it is therefore a sensitive indicator of the presence of pulmonary congestion and left-sided CHF. PCWP is not equal to LVEDP in the following situations:  
PCWP > LVEDP:  
- Mitral stenosis  
- Patient receiving PEEP  
- Left atrial myxoma  
- Pulmonary venous obstruction  
PCWP < LVEDP:  
- “Stiff” left ventricle  
- ↑ LVEDP (>25 mm Hg) | ↑: Left ventricular failure w/resultant pulmonary congestion, acute mitral insufficiency, tamponade  
↓: Left ventricular compliance (hypertrophy, infarction) |
| Cardiac output (CO) | 3.5-7 L/min | CO = SV × HR | ↓: Cardiac dysrhythmias, ↓ contracting muscle mass (myocardial ischemia, MI), mitral insufficiency, VSD |
| Cardiac index (CI) | 2.5-4 L/m² | CI relates CO to BSA  
CI = CO/BSA | ↑: High-output failure secondary to fluid overload, hepatocellular failure, renal disease, septic shock  
↓: Hypovolemia, cardiogenic shock, PE, hypothyroidism, CHF w/failing ventricle |
| Systemic vascular resistance (SVR) | 900-1300 dyne-sec/cm⁻⁵ | Resistance against which the left ventricle must work to eject its SV  
SVR = (MAP - RAP) × 80/CO | ↑: Hypervolemic vasoconstrictive states (HTN, cardiogenic shock, traumatic shock)  
↓: Septic shock, acute renal failure, pregnancy |
| Pulmonary vascular resistance (PVR) | 155-255 dyne-sec/cm⁻⁵ | PVR = (PAP - PAWP) × 80/CO | ↑: Cor pulmonale, PE, valvular heart disease, CHF  
↓: Hypervolemic states, pregnancy |
3. **Box 1-3** describes hemodynamic measurements in specific disease states.

4. **Table 1-12** illustrates the effects of therapeutic measures on hemodynamic measurements.

### Table 1-12: Effects of Therapeutic Measures on Hemodynamic Measurements

<table>
<thead>
<tr>
<th>Therapeutic Measure</th>
<th>CO</th>
<th>SVR</th>
<th>PCWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV fluids</td>
<td>N↑</td>
<td>N↑</td>
<td>↑</td>
</tr>
<tr>
<td>Diuretics</td>
<td>N↓↓</td>
<td>↓/Secondary↑</td>
<td>↓</td>
</tr>
<tr>
<td>Nitrates</td>
<td>N↑↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>↑</td>
<td>↓↓</td>
<td>N/↓</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>N↑↑</td>
<td>↑↑</td>
<td>N/↑↑</td>
</tr>
<tr>
<td>Dopamine</td>
<td>↑↑</td>
<td>↓</td>
<td>N/↓</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>↑↑</td>
<td>↓</td>
<td>N/↓</td>
</tr>
</tbody>
</table>

N, no effect.

### Box 1-3: Hemodynamic Measurements in Specific Disease States

- **Septic shock**
  - Early: ↓ PCWP, ↓ SVR, ↑ CO
  - Late: ↓ PCWP, ↑ SVR, ↓ CO
- **Neurogenic shock**: ↓ PCWP, ↓ SVR, N/↑ CO
- **Cardiac tamponade**: ↑ PCWP, ↑ SVR, ↓ CO, ↓ CI
- **CVP = PADP = PCWP**
- **Pulmonary embolism**: normal PCWP, ↑ PADP, ↓ CI
- **Cardiogenic shock**: ↑ PCWP, ↑ PADP, ↓ CO, ↓ CI, ↑ SVR
- **Hypovolemic shock**: ↓ PCWP, ↓ CO, ↑ SVR, ↓ CI
- **Right ventricular infarct**: RAP/PCWP ≥ 0.8

N, no effect.

### Figure 1-11

Basic spirometry. Lung volumes obtained with a bell spirometer.
4 PULMONARY FUNCTION TESTS

1. Indications:
   a. Physiologic assessment leading to dx
   b. Establishment of severity
   c. Monitoring of the disease process and response to Rx
   d. Bronchoprovocation
   e. Preoperative risk assessment
   f. Pulmonary disability
   g. Exercise testing

2. PFTs:
   a. Prebronchodilator and postbronchodilator spirometry (Fig. 1-11)
   b. Maximal expiratory flow-volume curve (Fig. 1-12)
   c. Pulse oximetry, resting

3. Interpretation of basic PFTs: Figure 1-13 and Table 1-13.

![Flow-volume curves of restrictive disease and various types of obstructive diseases compared with normal curves. FVC, forced vital capacity.](image1)

**FIGURE 1-12.** Flow-volume curves of restrictive disease and various types of obstructive diseases compared with normal curves. FVC, forced vital capacity.

![Timed vital capacity (or forced expirogram) using bellows or electronic spirometer. FEF, forced expiratory flow; FEV 1.0, forced expiratory volume in 1 sec; FVC, forced vital capacity.](image2)

**FIGURE 1-13.** Timed vital capacity (or forced expirogram) using bellows or electronic spirometer. FEF, forced expiratory flow; FEV 1.0, forced expiratory volume in 1 sec; FVC, forced vital capacity.
TABLE 1-13  Severity Determination

<table>
<thead>
<tr>
<th>Obstruction</th>
<th>FEV₁ % Predicted</th>
<th>Restriction</th>
<th>TLC % Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>65-79</td>
<td>Mild</td>
<td>70-79</td>
</tr>
<tr>
<td>Moderate</td>
<td>50-64</td>
<td>Moderate</td>
<td>60-69</td>
</tr>
<tr>
<td>Moderately severe</td>
<td>35-49</td>
<td>Moderately severe</td>
<td>50-59</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;35</td>
<td>Severe</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 sec; TLC, total lung capacity.

5 MECHANICAL VENTILATION

Indications for Mechanical Ventilation

1. Clinical assessment: presence of apnea, tachypnea (>40 bpm), or respiratory failure that cannot be adequately corrected by any other means.
2. Clinical instability, failure to protect the airway—usually from declining mental status.
3. ABGs: severe hypoxemia despite high-flow oxygen or significant CO₂ retention (e.g., oxygen tension [PO₂] <50, carbon dioxide tension [PCO₂] >50).
4. Physiologic parameters are of limited use because many pts w/respiratory insufficiency are unable to perform PFTs and their respiratory failure mandates immediate intervention. Some of the commonly accepted physiologic parameters for intubation and respiratory support are as follows:
   a. VC <10 mL/kg
   b. Inspiratory force 25 cm H₂O or less
   c. FEV₁ <10 mL/kg
   d. Tidal volume <5 mL/kg BW
   e. Minute ventilation >10 L/min
   f. Ratio of RR (breaths/min) to tidal volume (L) >105

Note: The clinical assessment is the most important determinant of the need for mechanical ventilation because neither physiologic parameters nor ABGs distinguish between acute and chronic respiratory insufficiency (e.g., a PCO₂ >60 mm Hg and an RR >30/min may be the “norm” for a patient w/COPD, whereas the same values in a young, otherwise healthy adult are indications for intubation and mechanical ventilation).

ICU Sedation

Commonly used agents are GABA agonists such as propofol and benzo. These agents can cause respiratory depression and delirium. The α-adrenoreceptor agonist dexmedetomidine (Precedex) is as effective for sedation but significantly better in incidence of delirium.

Common Modes of Mechanical Ventilation

Invasive mechanical ventilation is defined as ventilatory support supplied through endotracheal intubation. The use of devices that apply intermittent negative extrathoracic pressure or furnish intermittent positive pressure through a tight-fitting nasal or face mask w/o an artificial airway in place is known as noninvasive ventilation. The delivery of gas under positive pressure into the airways and the lungs is known as positive-pressure ventilation (Table 1-14).

1. IMV: The patient is allowed to breathe spontaneously, and the ventilator delivers a number of machine breaths at a preset rate and volume.
   a. Advantages and indications:
      i. IMV is indicated in the majority of spontaneously breathing pts because it maintains respiratory muscle tone and results in less depression of cardiac output than with ACV.
      ii. It is useful for weaning because as the IMV rate is decreased, the patient gradually assumes the bulk of the breathing work.
   b. Disadvantages:
      i. The increased work of breathing results in increased oxygen consumption (deleterious to pts w/myocardial insufficiency).
      ii. IMV is not useful in pts w/depressed respiratory drive or impaired neurologic status.
TABLE 1-14  **Modes of Positive-Pressure Ventilation**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
<th>Advantages and Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled mechanical ventilation (CMV)</td>
<td>Ventilator f, inspiratory time, and Vt (and thus Ve) preset</td>
<td>Can be used in patients w/sedation or paralysis; ventilator cannot respond to ventilatory needs</td>
</tr>
<tr>
<td>Assisted mechanical ventilation (AMV) or assist-control ventilation (ACV)</td>
<td>Ventilator Vt and inspiratory time preset, but patient can ↑ f (and thus Ve)</td>
<td>Ventilator may respond to ventilatory needs; ventilator may undertrigger or overtrigger, depending on sensitivity</td>
</tr>
<tr>
<td>Intermittent mandatory ventilation (IMV)</td>
<td>Ventilator delivers preset Vt, f, and inspiratory time, but patient also can breathe spontaneously</td>
<td>May ↓ asynchronous breathing and sedation requirements; ventilator cannot respond to ventilatory needs</td>
</tr>
<tr>
<td>Synchronized intermittent mandatory ventilation (SIMV)</td>
<td>Same as IMV, but ventilator breaths delivered only after patient finishes inspiration</td>
<td>Same as IMV, and patient not overinflated by receiving spontaneous and ventilator breaths at same time</td>
</tr>
<tr>
<td>High-frequency ventilation (HFV)</td>
<td>Ventilator f is ↑ and Vt may be smaller than Vd</td>
<td>May reduce peak airway pressure; may cause auto-PEEP</td>
</tr>
<tr>
<td>Pressure support ventilation (PSV)</td>
<td>Patient breathes at own f; Vt determined by inspiratory pressure and Crs</td>
<td>↑ comfort and ↓ work of breathing; ventilator cannot respond to ventilatory needs</td>
</tr>
<tr>
<td>Pressure control ventilation (PCV)</td>
<td>Ventilator peak pressure, f, and respiratory time preset</td>
<td>Peak inspiratory pressures may be ↓; hypoventilation may occur</td>
</tr>
<tr>
<td>Inverse ratio ventilation (IRV)</td>
<td>Inspiratory time exceeds expiratory time to facilitate inspiration</td>
<td>May improve gas exchange by ↑ time spent on inspiration; may cause auto-PEEP</td>
</tr>
<tr>
<td>Airway pressure release ventilation (APRV)</td>
<td>Patient receives CPAP at high and low levels to simulate Vt</td>
<td>May improve oxygenation at lower airway pressure; hypoventilation may occur</td>
</tr>
<tr>
<td>Proportional assist ventilation (PAV)</td>
<td>Patient determines own f, Vt, pressures, and flows</td>
<td>May amplify spontaneous breathing; depends entirely on patient’s respiratory drive</td>
</tr>
</tbody>
</table>

Crs, respiratory system compliance; f, respiratory rate; Vd, dead space; Ve, minute ventilation; Vt, tidal volume.

iii. It was previously assumed that the degree of respiratory muscle rest was proportional to the level of machine assistance. However, recent evidence indicates that respiratory-sensor output does not adjust to breath-to-breath changes in respiratory load, and IMV may therefore contribute to the development of respiratory muscle fatigue or prevent recovery from it.

2. **ACV**: The patient breathes at his or her own rate, and the ventilator senses the inspiratory effort and delivers a preset tidal volume (VT) w/each patient effort; if the patient’s RR decreases past a preset rate, the ventilator delivers tidal breaths at the preset rate.

a. Advantages and indications: useful in pts w/neuromuscular weakness or CNS disturbances.

b. Disadvantages:

i. Tachypnea may result in significant hypocapnia and respiratory alkalosis.

ii. Improper setting of sensitivity to the negative pressure necessary to trigger the ventilator may result in “fighting the ventilator” when the sensitivity is set too low.

iii. Increased sensitivity may result in hyperventilation; sensitivity is generally set so that an inspiratory effort of 2 to 3 cm will trigger ventilation.
iv. The respiratory muscle tone is not well maintained in pts on ACV, and this may result in difficulty w/weaning.

3. **CMV**: The patient does not breathe spontaneously; the RR is determined by the physician; the ventilator assumes all respiratory work by delivering a preset volume of gas at a preset rate.

a. Advantages and indications:
   i. Useful in pts who are unable to make an inspiratory effort (e.g., severe CNS dysfunction) and in pts w/excessive agitation or breathing effort.
   ii. Pts w/excessive agitation are often sedated w/morphine or benzo and paralyzed w/pancuronium bromide (Pavulon); adequate sedation is necessary to eliminate awareness of paralysis.
   iii. Initial pancuronium dose is 0.08 mg/kg IV in adults.
   iv. Later incremental doses starting at 0.01 mg/kg may be used as necessary to maintain paralysis; pancuronium should be administered only by or under the supervision of experienced clinicians; a combination of neostigmine and atropine may be used to reverse the action of the pancuronium.

b. Disadvantages: paralyzed pts on CMV must be closely monitored because ventilator malfunction or disconnection is rapidly fatal.

4. **SIMV**: A hybrid of ACV and IMV, the ventilator delivers a number of specified breaths/min (as w/IMV). However, at the appropriate interval (e.g., q6sec if machine rate is 10 breaths/min), the machine waits for an ET pressure deflection to signal patient effort and then delivers a positive-pressure breath; ventilator breaths are thus synchronized w/patient respiratory efforts, as w/assist features of ACV.

5. Other useful ventilation modes are as follows:

a. **Pressure control ventilation (PCV)**: A ventilatory mode in which inspiratory pressure, RR, and inspiratory time (Ti) are determined by the ventilator settings. Because inspiratory pressure is the controlled variable, VT during PCV is influenced by the mechanical properties of the respiratory system (resistance and compliance).

b. **Pressure support ventilation (PSV)**: A ventilatory mode in which the patient’s inspiratory effort is supported by a set level of inspiratory pressure. This pressure is maintained until respiratory flow falls below a threshold value, signaling the onset of expiration. VT during PSV is determined by patient effort and the mechanical properties of the lung. PSV differs from PCV in that the RR and the Ti are determined by the patient.

c. **Inverse ratio ventilation (IRV)**: A ventilatory strategy in which the inspiratory-to-expiratory ratio is prolonged to 1:1 or greater. In pts w/ARDS, IRV is used to improve oxygenation by increasing mean airway pressure. This modality is used as a salvage Rx when adequate oxygenation cannot be achieved w/conventional ventilation in ARDS. When used, pressure cycled IRV is preferred because of decreased barotrauma risk.

d. **Noninvasive positive-pressure ventilation (NPPV)**: Ventilatory support is delivered by use of a mechanical ventilator connected to a mouthpiece or mask instead of an ETT. It is very useful in pts w/chronic respiratory failure caused by neuromuscular disease or thoracic deformities and in pts w/idiopathic hypoventilation. It improves the patient’s well-being and may eliminate the need for tracheostomies. It is also used in pts as a short-term bridge to avoid intubation and mechanical ventilation, when possible, in conditions that are rapidly reversible, like hypercarbic respiratory failure in COPD and, importantly, acute pulmonary edema in heart failure. It is also sometimes used as salvage Rx in pts w/any of the indications for intubation who do not want to be intubated.

**Selection of Ventilator Settings**

1. VT: 10 to 15 mL/kg of ideal BW.
2. Rate (number of tidal breaths delivered per minute): 8 to 16, depending on the desired PaCO₂ or pH (increased rate equals decreased PaCO₂).
3. Mode: IMV, ACV, CMV (or PCV or PSV, depending on what is available at one’s institution).
4. Oxygen concentration (FiO<sub>2</sub>): the initial FiO<sub>2</sub> should be 100% unless it is evident that a lower FiO<sub>2</sub> will provide adequate oxygenation. The FiO<sub>2</sub> should be calibrated down as quickly as possible to prevent oxygen toxicity.
5. Obtain ABGs 15 to 30 minutes after initiation of mechanical ventilation.
6. Immediate CXR is indicated after intubation to evaluate for correct placement of ETT.
7. Sedation orders (e.g., morphine, diazepam) are necessary in most pts.
8. PEEP:
   a. The application of PEEP may prevent the closure of edematous small airways; it is indicated when arterial oxygenation is inadequate (saturation <90%) despite an FiO<sub>2</sub> >50%; it is useful in pts w/diffuse lung edema and refractory hypoxemia caused by intrapulmonary shunting (e.g., ARDS). Useful to ↓ the needed FiO<sub>2</sub> to ↓ oxygen toxicity. In reality, at least 5 mm PEEP is used on virtually everyone, but it can be ↓ if oxygenation is not a problem but intubation-associated hypotension is.
   b. PEEP is generally started at 5 cm H<sub>2</sub>O and ↑ by increments of 2 to 5 cm to maintain the Pao<sub>2</sub> at 60 mm Hg or greater.
   c. The use of PEEP can result in pulmonary barotrauma and hemodynamic compromise (secondary to decreased right ventricular filling).
   d. Pts receiving PEEP should have their cardiac output frequently monitored; the measurement of mixed venous oxygen saturation is useful to evaluate the effect of PEEP on cardiac output. The surrogate of cardiac output (BP) is fine in most pts.
9. Adjust the initial ventilator setting according to results of the ABGs and clinical response.
   a. Use the lowest FiO<sub>2</sub> necessary to maintain a Pao<sub>2</sub> >60 mm Hg (90% Hgb saturation in pts w/nl pH).
   b. Adjust minute ventilation (VT time rate) to normalize the pH and the Paco<sub>2</sub>.
      i. ↑ the VT or the rate will ↓ Paco<sub>2</sub> and ↑ pH.
      ii. Do not lower the Paco<sub>2</sub> below the “norm” for that patient (e.g., some pts w/COPD should be allowed to maintain their usual mildly elevated Paco<sub>2</sub> to avoid alkalosis and to provide stimulus for breathing).
10. Common ventilator machine settings for various disorders are described in Table 1-15.

---

**TABLE 1-15** Common Ventilator Machine Settings for Various Disorders

<table>
<thead>
<tr>
<th>Condition</th>
<th>Mode</th>
<th>VT, VE</th>
<th>PEEP (cm H&lt;sub&gt;2&lt;/sub&gt;O)</th>
<th>Pressure Targets</th>
<th>FiO&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed CNS drive</td>
<td>Mandatory</td>
<td>VT = 10 mL/kg VE = 6-8 L/min</td>
<td>0-5</td>
<td>Peak usually &lt;35 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>Minimum for Sao&lt;sub&gt;2&lt;/sub&gt; &gt;90%</td>
</tr>
<tr>
<td>Neuromuscular insufficiency</td>
<td>Acute: mandatory ACV, SIMV</td>
<td>VT = 8-10 mL/kg VE = 6-8 L/min</td>
<td>0-5</td>
<td>Peak usually &lt;35 cm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>As above</td>
</tr>
<tr>
<td></td>
<td>Mild, recovering: SIMV and PSV, PSV alone</td>
<td>Guarantee VT &gt;350 mL w/PSV breaths</td>
<td>0-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>Early: ACV, SIMV Late: see text</td>
<td>VT = 8 mL/kg VE: minimize, usually 8-10 L/min Peak flow ≥60 L/min</td>
<td>0*</td>
<td>Plateau &lt;30 cm H&lt;sub&gt;2&lt;/sub&gt;O; monitor for intrinsic PEEP (auto-PEEP)</td>
<td>As above</td>
</tr>
</tbody>
</table>

*PEEP added to obstructive disease only in special circumstances.
Major Complications of Mechanical Ventilation

1. Pulmonary barotrauma (e.g., pneumomediastinum, pneumothorax, SC emphysema, pneumoperitoneum): generally secondary to high levels of PEEP, excessive tidal volumes, high peak airway pressures, and coexistence of significant lung disease.

2. Pulmonary thromboemboli can be prevented by vigorous leg care, antiembolic stockings, and use of prophylactic low-dose heparin (i.e., 5000 U SC q8-12h).

3. GI bleeding: prophylaxis w/IV ranitidine 50 mg q8h, PPIs, or sucralfate suspension, 1 g q6h through NG tube, is indicated in most pts on mechanical ventilators.

4. Arrhythmias: avoid the use of arrhythmogenic drugs and prevent rapid acid-base shifts.

5. Accumulation of large amount of secretions: frequent respiratory toilet is necessary in all pts on mechanical ventilators. Consider mouth care with chlorhexadine.

6. Others: nosocomial infections, laryngotracheal injury, malnutrition, hypophosphatemia, oxygen toxicity, psychosis; risk factors for pneumonia are severe illness, old age (>60 years), prior administration of abx, supine head position. Respiratory ICU pts who are managed in the semirecumbent (30- to 45-degree head-up) position have a lower incidence of nosocomial pneumonia. Use of sucralfate rather than H₂ antagonists is also associated with/lower incidence of nosocomial pneumonia. Extubation as rapidly as possible is important to help prevent ventilator-associated pneumonia.

Withdrawal of Mechanical Ventilatory Support

1. Common criteria for ventilator weaning:
   a. Improved clinical status (the patient is alert and hemodynamically stable); process that required mechanical ventilation is reversed.
   b. Adequate oxygenation (PaO₂ >60 mm Hg w/inspired oxygen concentration of 40%).
   c. pH 7.33 to 7.48 w/acceptable PaCO₂.
   d. RR of 25 breaths/min or less.
   e. VC of 10 mL/kg or more.
   f. Resting minute ventilation <10 L/min, w/ability to double the resting minute ventilation.
   g. Peak pressure more negative than −25 cm H₂O.
   h. Vt >5 mL/kg.
   i. The ratio of respiratory frequency to Vt during 1 minute of spontaneous breathing, also known as the rapid shallow breathing index (f/Vt), is a good predictor of a patient’s readiness for weaning; a value of fewer than 100 breaths/min/L indicates that weaning probably will be successful, especially if it is confirmed by serial measurements.

Note: The preceding criteria are only guidelines; significant variation may be present (e.g., an RR of 30 breaths/min may be acceptable in a patient w/COPD). Failure to meet these criteria does not mean that the patient will not be weaned successfully.

2. Methods of weaning:
   a. Weaning by IMV
      i. Gradually decrease the IMV as tolerated (e.g., two breaths q3-4h), monitoring ABGs PRN. Monitoring of clinical signs (RR, patient’s comfort, and tidal volume) is usually sufficient to avoid repeated ABGs.
      ii. Do not change more than one parameter at a time.
      iii. When the patient is tolerating an IMV of 4 to 6, a trial w/T tube can be attempted. The T tube is attached to the ETT and delivers humidified oxygen (FiO₂ 40%).
      iv. If the patient tolerates the T tube well, extubation may be attempted.
         (a) Have adequate equipment and personnel available if reintubation is necessary (start early in the day).
(b) Suction airway and oropharynx.
(c) Deflate cuff and extubate.
(d) Administer oxygen by face mask (FIO₂ 40%-100%).
(e) Auscultate the lungs for adequate air movement.
(f) Closely monitor VS.
(g) Obtain ABGs approximately 15 to 30 minutes after extubation.

v. Reintubate if extubation is poorly tolerated.
b. Stable pts w/o pulmonary disease and w/good probability of quick extubation (e.g., after uncomplicated cardiac surgery) may be given a direct trial of T tube (bypassing gradual decreases of IMV).
c. PSV
   i. Titrate pressure to achieve a frequency of 25 breaths/min or fewer; allow a CPAP of 5 cm of water or less.
   ii. Set pressure support initially at 18.0 ± 6.1 cm of water and attempt to reduce this level of support by 2 to 4 cm of water at least bid.
   iii. Extubate pts who tolerate a pressure support setting of 5 cm of water for 2 hours w/no apparent ill effects.
d. Intermittent trials of spontaneous breathing
   i. Disconnect stable patient from the ventilator and allow the patient to breathe spontaneously through either a T-tube circuit or a continuous-flow circuit designed to provide a CPAP of 5 cm of water or less.
   ii. Attempt the trial at least bid and gradually increase the duration of the trial.
   iii. Provide ACV for at least 1 hour between the trials.
   iv. Extubate pts who are able to breathe on their own for at least 2 hours w/o signs of distress.
e. Once-daily trial of spontaneous breathing
   i. Disconnect the stable patient from the ventilator and allow him or her to breathe spontaneously through a T-tube circuit for up to 2 hours each day.
   ii. Extubate pts who tolerate a 2-hour trial w/o signs of distress.
   iii. Reinstitute ACV for 24 hours if signs of intolerance develop.

**Failure to Wean from Mechanical Ventilator**

Failure usually results from premature attempts at weaning (e.g., patient is hemodynamically unstable). Other common, reversible causes of failure to wean are as follows:

1. Hypophosphatemia, hypomagnesemia, hypokalemia.
2. Drug toxicity (e.g., excessive CNS depression from analgesics, sedatives). Continuous infusions of sedative drugs may prolong the duration of mechanical ventilation. Daily interruption of sedative infusions until the patient is awake decreases the duration of mechanical ventilation.
4. Excessive secretions.
5. Significant acid-base disturbances (e.g., metabolic alkalosis depresses respiratory drive).
6. Hypothyroidism.
7. Malnutrition.
8. Small-bore ETT (tube ≥8 mm is preferred).
9. Interference w/ chest wall (e.g., chest tube, restraints).

**Ventilator-Associated Pneumonia**

1. Ventilator-associated pneumonia occurs in 9% to 24% of pts intubated >48 hours.
2. The etiology of ventilator-associated pneumonia varies w/the following factors:
   a. Onset <5 days after hospital admission or intubation.
   b. Presence of risk factors (previous recent abx treatment, corticosteroid use, structural lung disease, and immunosuppression).
3. Pts w/pneumonia diagnosed <5 days after hospital admission or intubation and w/no risk factors can be empirically treated w/one of the following abx:
   a. Second- or third-generation cephalosporin
   b. β-Lactam w/ or w/o β-lactamase inhibitors
   c. Quinolones
4. Pts w/risk factors or those diagnosed 5 days or more after hospital admission or intubation can be empirically treated w/two abx from the following classes:
   a. Antipseudomonal lactam agents (e.g., imipenem, meropenem, cefepime, ceftazidime, piperacillin-tazobactam)
   b. Quinolones w/reliable antipseudomonal activity
   c. Aminoglycoside
5. Consider addition of vancomycin in institutions w/MRSA.
6. Recommended duration of treatment is 7 days, longer if *Pseudomonas* infection is diagnosed.

### 6 PACEMAKERS

1. Classification: Table 1-16.
2. Indications for pacemaker in MI: Table 1-17.

<table>
<thead>
<tr>
<th>TABLE 1-16</th>
<th>Commonly Programmed Modes of Pacemaker Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAI</td>
<td>Demand atrial pacing; output inhibited by sensed atrial signals</td>
</tr>
</tbody>
</table>
| AAIR | Demand atrial pacing; output inhibited by sensed atrial signals
   Atrial pacing rates ↓ and ↑ in response to sensor input up to the programmed sensor-based upper rate |
| VVI | Demand ventricular pacing; output inhibited by sensed ventricular signals |
| VVIR | Demand ventricular pacing; output inhibited by sensed ventricular signals
   Ventricular paced rates ↓ and ↑ in response to sensor input up to the programmed sensor-based upper rate |
| VDD | Paces ventricle, senses in both atrium and ventricle
   Synchronizes w/atrial activity and paces ventricle after a preset atrioventricular interval up to the programmed upper rate |
| VDDR | Paces ventricle, senses in both atrium and ventricle
   Synchronizes w/atrial activity and paces ventricle after a preset atrioventricular interval up to the programmed upper rate; in absence of spontaneous atrial activity, functions as VVIR |
| DDD | Paces and senses in both atrium and ventricle
   Paces ventricle in response to sensed atrial activity up to programmed upper rate |
| DDDR | Atrial and ventricular paced rates can both ↑ and ↓ in response to sensor input up to the programmed sensor-based upper rate |

A, atrium; V, ventricle; D, dual (both atrium and ventricle); I, inhibition and triggering (pacing in response to another event); R, rate adaptation available.

### 7 PROSTHETIC HEART VALVES

Artificial valves can be mechanical or biologic.

1. **Mechanical prosthetic valves**: Preferred valve substitutes in adult pts who are already taking anticoagulants (e.g., for AF). The most important risk linked to these valves is valvular thrombosis requiring lifelong anticoagulation.
   a. **Ball-cage prosthesis**: Constructed as a ball in a metallic cage (e.g., Starr-Edwards valve). The ball prosthesis partially obstructs blood flow, and flow through the prosthesis is turbulent. Benefit: low cost. Disadvantage: trauma to RBCs can result in hemolytic anemia. Prosthesis is also very bulky.
   b. **Tilting disk prosthesis**: The mobile element of these valves is a tilting disk held in place by two welded struts. Older models consisted of the Bjork-Shiley valve; a newer model is the Medtronic Hall Omnicarbon prosthesis.
TABLE 1-17 Guidelines of the ACC and the AHA for Temporary or Permanent Implantation of Pacemakers in Patients with Acute MI

<table>
<thead>
<tr>
<th>Class*</th>
<th>Indications for Temporary Pacing</th>
<th>Indications for Permanent Pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Asystole</td>
<td>Persistent second-degree AV block in the His-Purkinje system, with bilateral BBB or third-degree AV block within or below the His-Purkinje system after MI</td>
</tr>
<tr>
<td></td>
<td>Symptomatic bradycardia (including sinus bradycardia or Mobitz type I block with hypotension)</td>
<td>Transient advanced (second- or third-degree) infranodal AV block and associated BBB† Persistant and symptomatic second- or third-degree AV block</td>
</tr>
<tr>
<td></td>
<td>Bilateral BBB (alternating BBB or RBBB alternating with LAFB or LPFB)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bifascicular block that is new or of indeterminate age (RBBB with LAFB or LPFB or LBBB) with a prolonged PR interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mobitz type II second-degree AV block</td>
<td></td>
</tr>
<tr>
<td>IIa</td>
<td>RBBB and LAFB or LPFB that is new or of indeterminate age</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>RBBB with a prolonged PR interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LBBB that is new or of indeterminate age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurring sinus pauses not responsive to atropine</td>
<td></td>
</tr>
<tr>
<td>IIb</td>
<td>Bifascicular block of indeterminate age</td>
<td>Persistent second- or third-degree AV block at the level of the AV node</td>
</tr>
<tr>
<td></td>
<td>Isolated RBBB that is new or of indeterminate age</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Prolonged PR interval</td>
<td>Transient AV conduction disturbances in the absence of intraventricular conduction defects</td>
</tr>
<tr>
<td></td>
<td>Type I second-degree AV block with normal hemodynamics</td>
<td>Persistent first-degree AV block in the presence of BBB that is old or of indeterminate age</td>
</tr>
<tr>
<td></td>
<td>Accelerated idioventricular rhythm</td>
<td>Acquired LAFB in the absence of AV block</td>
</tr>
<tr>
<td></td>
<td>BBB or fascicular block known to exist before acute MI</td>
<td></td>
</tr>
</tbody>
</table>

LAFB, left anterior fascicular block; LPFB, left posterior fascicular block.
*Class designations refer to the level of evidence supporting the effectiveness of the procedure or treatment, where class I indicates that the evidence is very strong and class III that it is absent or that the procedure is not useful and may be harmful.
†An electrophysiologic study may be useful to determine the site of the block.

c. **Bileaflet prostheses:** Made of two semicircular pivoting disks constructed from pyrolytic carbons, a material considered to be less thrombogenic. Introduced in 1977, the prototype is the St. Jude valve, the most commonly implanted prosthetic valve. Newer models include the CarboMedics prosthesis.

2. **Biologic valves:** These valves are divided into three groups based on the origin of the biologic material: heterografts (animal origin), homografts (human donor), and autografts (tissues originating from the patient).
   a. **Bioprostheses (heterografts):** Porcine bioprosthetic valves such as the Carpentier-Perimount are derived from pig aortic leaflets mounted on metal-coated stents. A major concern in these valves is degradation over time, usually manifested as a valvular leak caused by a torn and prolapsed cusp or by commissural detachment. As a rule, most pts >75 years of age are offered a bioprosthesis.
   b. **Homograft valves:** Valves harvested from human donors. They have an excellent hemodynamic profile and are particularly useful in the management of infectious endocarditis because of the absence of prosthetic material.
c. **Autograft valves:** The main use of autograft valves is the transfer of the pulmonary valve to the aortic position (Ross procedure) w/the subsequent implantation of a pulmonary homograft into the prior position of the pulmonary valve. The Ross procedure is the operation of choice for aortic valve replacement.

### E. Procedures

#### 1 LUMBAR PUNCTURE

**Indications**
1. Suspected meningitis.
2. Suspected encephalitis.
3. Dx of meningeal carcinomatosis and meningeal leukemia.
4. Dx of tertiary syphilis.
5. Follow-up of Rx for meningitis (selected cases).
6. Evaluation for GBS.
7. Evaluation for MS.
8. Staging of lymphomas.
9. Evaluation of dementia (in selected cases).
10. Treatment of pseudotumor cerebri.
11. Suspected subarachnoid hemorrhage (only after nl head CT scan).
12. Introduction of drugs, anesthetics, or radiographic media into the CNS.

**Contraindications**
1. Infection at the site of LP.
2. ↑ ICP.
3. Severe hemorrhagic diathesis (hereditary or acquired).
4. Presence of a CNS mass lesion.
5. Suspected venous sinus occlusion.
6. Uncooperative patient.

**Procedure**
1. Perform a careful ophthalmoscopic examination; if ↑ ICP or a CNS space-occupying lesion is suspected, CT scan of the head should be done before LP.
2. Place the patient in a lateral decubitus position w/spine flexed (draw shoulders forward and bring thighs toward the abd; maximal flexion of the spine helps open up the interspace and improves chances of a successful procedure). If the patient is able to, LP can also be performed w/the patient sitting upright, ideally leaning over a tray table.
3. Identify the L4-5 interspace (imaginary line connecting the iliac crests).
4. Clean area w/povidone-iodine solution.
5. Anesthetize skin and SC tissues w/1% to 2% lidocaine.
6. Gently introduce the spinal needle (w/bevel turned upward) in the L4-5 interspace in a horizontal direction and w/slight cephalad inclination. Point toward the umbilicus. A drop in resistance may be felt as the needle penetrates the dura.
7. Measure opening pressure (nl is 100 to 200 mm Hg [10 to 20 cm Hg]).
   a. If the pressure is elevated, instruct the patient to relax and ensure that there is no abd compression or breath holding (straining and pressure on the abd wall will ↑ CSF pressure).
   b. If the pressure is markedly elevated, remove only 5 mL of spinal fluid and remove the spinal needle immediately.
8. Collect 5 to 10 mL of spinal fluid in four collection tubes (2 mL/tube).
9. Measure closing pressure, then remove manometer and stopcock, and replace stylet before removing the spinal needle; apply pressure to the puncture site w/sterile gauze for a few minutes.
10. Instruct the patient to remain in a horizontal position for approximately 4 hours to minimize post-LP headache (caused by CSF fluid leakage through the puncture site).
11. Process the CSF fluid.
   a. Tube 1: protein, glucose.
   b. Tube 2: Gram stain of the centrifuged specimen.
c. Tube 3: save the fluid until further notice.
d. Tube 4: cell count (total and diff).

12. Consider additional tests (if indicated).
a. Bacterial cultures in suspected bacterial meningitis.
b. Assay for cryptococcal antigen in immunocompromised pts.
c. Countercurrent immunoelectrophoresis or latex agglutination: to detect specific polysaccharide bacterial antigens (Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae) in the CSF of pts w/inconclusive Gram stain findings (e.g., pts w/partially treated meningitis).
d. Oligoclonal banding and assay for myelin basic protein are useful to diagnose MS.
e. VDRL, AFB stain, Wright stain of sediment, India ink preparation, Lyme titer Ab, fungal or viral cultures, and cytologic examination should be ordered only when specifically indicated.
f. The most sensitive technique for rapid dx of tuberculous meningitis is PCR assay. Bacteriologic methods are inadequate for early dx because there are generally too few organisms in the CSF for identification by direct smear, and identification w/cultures takes 6 to 8 weeks.
g. Rapid dx of herpes simplex encephalitis (when suspected) can be accomplished by nested PCR assay of CSF.
h. Enterovirus-specific reverse transcriptase PCR assay of CSF fluid is useful for rapid dx of enteroviral meningitis.

**Interpretation of Results**

1. Appearance of the fluid:
   b. Yellow color (xanthochromia) in the supernatant of centrifuged CSF within 1 hour or less after collection is usually the result of previous bleeding (subarachnoid hemorrhage); it may also be caused by increased CSF protein, melanin from meningeal melanomas, or carotenoids.
   c. Pinkish color is usually the result of a bloody tap; the color generally clears progressively from tubes 1-4 (the supernatant is usually crystal clear in traumatic taps).
   d. Turbidity usually indicates the presence of leukocytes (bleeding introduces approximately 1 white blood cell to 500 RBCs into the CSF).

2. CSF pressure: elevated pressure can be seen in pts w/meningitis, meningoencephalitis, pseudotumor cerebri, mass lesions, and intracerebral bleeding.

3. Cell count: in the adult, the CSF is normally free of cells (although up to 5 mononuclear cells/mm³ is considered nl); the presence of granulocytes is never nl.
   a. Neutrophils: seen in cases of bacterial meningitis, early viral meningoencephalitis, and early tuberculous meningitis.
   b. Increased lymphocytes: tuberculous meningitis, viral meningoencephalitis, syphilitic meningoencephalitis, fungal meningitis, Lyme disease, SLE, Listeria.

4. Protein: serum proteins are generally too large to cross the nl blood-CSF barrier; however, ↑ CSF protein is seen w/meningeal inflammation, traumatic tap, ↑ CNS synthesis, tissue degeneration, obstruction to CSF circulation, and GBS.

5. Glucose:
   a. ↓ glucose is seen w/bacterial meningitis, tuberculous meningitis, fungal meningitis, subarachnoid hemorrhage, and some cases of viral meningitis.
   b. A mild ↑ in CSF glucose level can be seen in pts w/very elevated serum glucose levels.

Note: Table 1-18 describes CSF abnormalities found in various CNS conditions.
Thoracentesis

**Indications**
1. Presence of any pleural effusion of unknown cause.
2. Relief of dyspnea caused by large pleural effusion.

**Contraindications**
1. Clotting abnormalities.
2. Thrombocytopenia.
3. Uncooperative patient or patient with severe cough or hiccups.

**Localization of Pleural Effusion**
1. Physical examination: dullness to percussion, loss of tactile fremitus.
2. CXR: PA view is usually sufficient in identifying the fluid collection; but in case of equivocal effusions, a lateral decubitus CXR can demonstrate layering out of the pleural fluid. Effusions >1 cm on a lateral decubitus film are usually sufficiently large to be removed at the bedside with additional imaging.
3. Fluoroscopy, ultrasonography, or CT guidance in performing thoracentesis if the fluid collection has the following qualities:
   a. <10 mm thick
   b. Not freely movable on the lateral decubitus x-ray view

**Procedure**
1. Position patient in a sitting position with arms and head supported on a bedside adjustable table.
2. Identify the area of effusion by gentle percussion.
3. Clean the area with povidone-iodine solution and maintain strict aseptic technique.
4. Insert the needle in the posterior chest (approximately 5 to 10 cm lateral to the spine, in the midpoint between the spine and the posterior axillary line) in 1 to 2 interspaces below the point of dullness to percussion.
5. Anesthetize the skin and SC tissues with 1% to 2% lidocaine using a 25-gauge needle.
6. Make sure that the needle is positioned and advanced above the superior margin of the rib (the intercostal nerve and the blood supply are located near the inferior margin). “Walk” the needle over the

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**TABLE 1-18 Cerebrospinal Fluid Abnormalities in Various CNS Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Appearance</th>
<th>Glucose (mg/dL)</th>
<th>Protein (mg/dL)</th>
<th>Cell Count (cells/mm³) and Cell Type</th>
<th>Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear</td>
<td>50-80</td>
<td>20-45</td>
<td>&lt;6 lymphocytes</td>
<td>100-200</td>
</tr>
<tr>
<td>Acute bacterial meningitis</td>
<td>Cloudy</td>
<td>↓↓</td>
<td>↑</td>
<td>↑, usually mononuclear cells; may be PMNs in early stages</td>
<td>N/↑</td>
</tr>
<tr>
<td>Aseptic (viral) meningitis</td>
<td>Clear/cloudy</td>
<td>N</td>
<td>↑</td>
<td>↑ PMNs (early) ↑ lymphocytes (later)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Bloody/xanthochromic</td>
<td>N/↓</td>
<td>↑</td>
<td>↑ RBCs</td>
<td>↑</td>
</tr>
<tr>
<td>Neoplasm</td>
<td>Clear/xanthochromic</td>
<td>N/↑</td>
<td>N↑</td>
<td>N/↑ lymphocytes</td>
<td>↑</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>Cloudy</td>
<td>↓</td>
<td>↑</td>
<td>↑ PMNs (early) ↑ lymphocytes (later)</td>
<td></td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>Clear/cloudy</td>
<td>↓</td>
<td>↑</td>
<td>↑ monocytes</td>
<td></td>
</tr>
<tr>
<td>Neurosyphilis</td>
<td>Clear/cloudy</td>
<td>N</td>
<td>↑</td>
<td>↑ monocytes N/↑</td>
<td>N</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
<td>Clear/cloudy</td>
<td>N</td>
<td>↑</td>
<td>N/↑ lymphocytes</td>
<td>N</td>
</tr>
</tbody>
</table>
superior margin of the rib and deeper into the interspace, anesthetizing the intercostal muscle layers.

7. Apply negative pressure as the needle is advanced. In thin pts, this needle is often sufficiently long to reach the pleural space. If pleural fluid is withdrawn, anesthetize the pleura adequately and note the depth at which it was reached. If it is not reached, use a longer 20- to 22-gauge syringe w/1% to 2% lidocaine, advance it slowly w/negative pressure along the same track as the prior needle, anesthetize the pleura adequately, and advance the needle into the pleural space. If the purpose of the thoracentesis is for dx only, a 30- to 50-mL syringe may then be attached and pleural fluid withdrawn for diagnostic studies. If the purpose of the thoracentesis is fluid removal, proceed further as below. Place a clamp on the needle at skin level to mark the depth, then remove the needle and note the depth of insertion needed for the thoracentesis needle.

8. In the previous puncture site, insert a 17-gauge needle (flat bevel) attached to a 30-mL syringe via a three-way stopcock connected to a drainage tube.

9. Slowly advance the needle (above the superior margin of the rib) and gently aspirate while advancing.

10. Keep a clamp or a hemostat on the needle at the level previously marked to prevent it from inadvertently advancing forward. Many thoracentesis kits will have a catheter that might be advanced over the needle to remove the risk of having a sharp needle within the pleural space.

11. Remove the necessary amount of pleural fluid (usually 100 mL for diagnostic studies), but do not remove more than 1000 mL of fluid at any one time because of ↑ risk of pulmonary edema or hypotension (pneumothorax from needle laceration of the visceral pleura is also much more likely to occur if an effusion is completely drained).

12. Gently remove the needle.

13. Obtain measurements of serum LDH, alb, glucose, and total protein levels.

14. Process the pleural fluid; the initial laboratory studies should be aimed only at distinguishing an exudate from a transudate (Fig. 1-14).
   a. Tube 1: protein, LDH, alb.
   b. Tubes 2, 3, 4: save the fluid until further notice. In selected pts w/suspected empyema, ascertaining a pH level may be useful (generally <7.0).

Note: Do not order further tests until the presence of an exudate is confirmed on the basis of protein and LDH determinations (see Table 1-19). However, if the results of protein and LDH determinations cannot be obtained within a reasonable time (resulting in unnecessary delay), additional laboratory tests should be ordered at the time of thoracentesis.

15. A serum/effusion alb gradient of 1.2 g/dL or less is indicative of exudative effusions, especially in pts w/CHF treated w/diuretics.

16. Note the appearance of the fluid:
   a. A grossly hemorrhagic effusion can be a result of a traumatic tap, a neoplasm, or an embolus w/infarction.
   b. A milky appearance indicates either of the following:
      i. Chylous effusion: caused by trauma or tumor invasion of the thoracic duct; lipoprotein electrophoresis of the effusion reveals chylomicrons and triglyceride levels >115 mg/dL.
      ii. Pseudochylous effusion: often seen w/chronic inflammation of the pleural space (e.g., tuberculosis, connective tissue diseases).

Complications
1. Pneumothorax.
2. Hemorrhage.
3. Vasovagal episode.
4. Infection.
5. Unilateral pulmonary edema.
6. Puncture of liver or spleen.
7. SC emphysema.
8. Air embolism.

**3 PARACENTESIS**

**Indications**
1. Ascites of undetermined etiology.
2. Evaluation for possible peritonitis.
3. Relief of abd pain and discomfort caused by tense ascites.
4. Relief of dyspnea caused by elevated diaphragm (from ascites).
5. Evaluation of possible intra-abd hemorrhage in a patient w/blunt abd trauma.
6. Institution of peritoneal dialysis.

**Contraindications**
1. Bleeding disorders, thrombocytopenia (relative contraindication).
2. Bowel distention.
3. Infection or surgical scars at the site of needle entry.
4. Acute abd.
5. Distended bladder that cannot be emptied w/Foley catheter.

**Procedure**
1. Have the patient empty the bladder (insertion of a Foley catheter is not recommended but may be necessary in certain pts).
2. To identify the site of paracentesis, first locate the rectus muscle; a good site is approximately 2 to 3 cm lateral to the rectus muscle border in the lower abd quadrants. Avoid the following:
   a. Rectus muscles (increased risk of hemorrhage from epigastric vessels)
   b. Surgical scars (increased risk of perforation caused by adhesion of bowel to the wall of the peritoneum)
   c. Areas of skin infection (increased risk of intraperitoneal infection)
   d. Note: an alternative site is on the linea alba 3 to 4 cm below the umbilicus.
3. Cleanse the area w/povidone-iodine and drape the abd.
4. Anesthetize the puncture site w/1% to 2% lidocaine.
5. Cautiously insert the needle (attached to a syringe) perpendicular to the skin; a small “pop” is felt as the needle advances through the anterior and posterior muscular fascia, and entrance into the peritoneal cavity is evidenced as a sudden “give” (use caution to avoid the sudden thrust forward of the needle). Some physicians use the Z technique to minimize leaks—the needle is inserted through the skin, then moved laterally before entering the peritoneal cavity to avoid a straight shot from skin to peritoneal cavity that is better for leaking fluid.
6. Remove the necessary amount of fluid (generally not more than 1 L, particularly in cirrhotic pts). If it is a therapeutic paracentesis w/plans to remove a significant amount of fluid, one can use an angiocatheter (basically just an IV) to cover the sharp needle during the procedure and to allow the operator to move the catheter around at will (in small increments) to try to restart flow when it stops. Transfusion of alb may be necessary with >4 to 5 L of paracentesis to avoid hemodynamic deterioration.
7. If it is a diagnostic paracentesis, process the fluid as follows:
   a. Tube 1: LDH, glucose, alb levels
   b. Tube 2: protein level, specific gravity
   c. Tube 3: complete blood cell count and diff
   d. Tube 4: save until further notice
9. Gram stain, AFB stain, bacterial and fungal cultures, amylase, and TGs should be ordered only when clearly indicated; bedside inoculation of blood culture bottles w/10 to 20 mL of ascitic fluid improves sensitivity in detecting bacterial growth in suspected cases of bacterial peritonitis.
10. If malignant ascites is suspected, consider ascertaining a carcinoembryonic antigen level on the paracentesis fluid and a cytologic evaluation.

**Interpretation of Results**
1. Peritoneal effusion, like pleural effusion, can be subdivided into exudative or transudative on the basis of its characteristics (Table 1-19).
2. The serum-ascites albumin gradient (SAAG) (serum alb level–ascitic fluid alb level) correlates directly w/portal pressure and can also be used to classify ascites (Table 1-20). Pts w/gradients of 1.1 g/dL or higher have ascites secondary to portal HTN, and those w/gradients <1.1 g/dL do not; the accuracy of this method is >95%.
3. Table 1-21 describes the characteristics of ascitic fluid in various conditions.
4. An ascitic fluid polymorphonuclear leukocyte count >500/µL is suggestive of SBP.
5. A blood–ascitic fluid alb gradient <1.1 g/dL is suggestive of malignant ascites.

**Complications**
1. Persistent leakage of ascitic fluid.
2. Hypotension and shock.
4. Perforated bowel.
5. Abscess formation in area of puncture site.
6. Peritonitis.
ARTROCENTESIS

Indications
1. Presence of effusion of unexplained etiology.
2. Steroid injection.
3. Decompression of a hemorrhagic effusion in traumatized joints.
4. Evaluation of abx response in pts w/infectious arthritis.
5. Removal of purulent fluid in distended infected joints.

Contraindications
1. Cellulitis or broken skin over the intended entry site.
2. Coagulopathy.
3. Unstable joint.

Procedure
1. Palpate the joint and identify the extensor surface (vessels and nerves are less commonly found here).
2. With firm pressure, use a ballpoint pen that has the writing portion retracted to mark the specific area of the joint to be aspirated.
3. Clean the skin w/an antiseptic solution.
4. Use a 25-gauge needle to infiltrate the skin w/1% to 2% lidocaine.
5. Gently insert an 18- or 20-gauge needle connected to a 20- to 30-mL syringe; a slight “pop” may be felt as the needle penetrates through the capsule.
6. Apply gentle suction to the syringe to aspirate the fluid.
7. Gently remove the needle and apply slight pressure to the puncture site.
8. Process the aspirated synovial fluid:
   a. Tube 1 (no heparin): viscosity, mucin clot
   b. Tube 2 (containing heparin): glucose level
   c. Tube 3 (containing heparin): Gram stain, C&S, cytology, CBC and diff
   d. Glass slide: place a drop of fluid and examine under polarized light
   e. Plate w/Thayer-Martin medium (used in cases of suspected gonococcal arthritis); assessment for Lyme titer, cultures for anaerobes, Mycobacterium tuberculosis, and fungi should be ordered only when clearly indicated.
9. Draw samples for measurement of serum glucose level.

Interpretation of Results
1. Color: normally it is clear or pale yellow; cloudiness indicates inflammatory process or presence of crystals, cell debris, fibrin, or TGs.
2. Viscosity: normally it has a high viscosity because of hyaluronate; when fluid is placed on a slide, it can be stretched to a string longer than 2 cm before separating (low viscosity indicates breakdown of hyaluronate [lysosomal enzymes from leukocytes] or the presence of edema fluid).
3. Mucin clot: add 1 mL of fluid to 5 mL of a 5% acetic acid solution and allow 1 minute for the clot to form; a firm clot (does not fragment on shaking) is nl and indicates the presence of large molecules of hyaluronic acid (this test is nonspecific and infrequently done).
4. Glucose level: normally it approximately equals serum glucose level; a difference of more than 40 mg/dL is suggestive of infection.
5. Total protein concentration is <2.5 g/dL in the nl synovial fluid; it is elevated in cases of inflammatory and septic arthritis.
6. Microscopic examination for crystals:
   a. Gout: monosodium urate crystals
   b. Pseudogout: calcium pyrophosphate dihydrate crystals

Note: synovial fluid is classified into three major groups on the basis of its characteristics (Table 1-22).

Complications
1. Infection.
2. Hemorrhage.
3. Tendon rupture.
5 RADIAL ARTERY CANNULATION (A-LINE)

Indications
1. Monitoring of BP during use of potent vasoactive agents (e.g., nitroprusside, dopamine).
2. Monitoring of BP in critically ill hypotensive pts (e.g., shock) or during major surgery (e.g., CV).
3. Frequent ABG analysis or other blood tests in pts w/limited vascular access.

Procedure
1. Evaluate patency of the ulnar artery w/the Allen test. Simultaneously compressing the radial and ulnar arteries, have the patient clenched and elevate the fist to let blood drain from the hand; keep pressure on both arteries until the hand blanches; then have the patient open the hand while pressure is maintained on both arteries. Release the ulnar artery and observe the hand for blushing. The presence of blushing and return of nl color to the hand indicate patency of the ulnar artery and adequate blood supply if radial occlusion occurs w/the catheter.
2. Hyperextend the hand over a wrist roll and immobilize it and the lower arm.
3. Sterile drape and clean the area w/povidone-iodine solution.
4. Anesthetize the skin and then insert the angiocatheter through the skin at a 30- to 45-degree angle, advancing it parallel to the artery; gently cannulate the artery (as evidenced by the blush of blood within the catheter). Advance the catheter over the needle until it locks into place. It should easily advance over the needle. If it does not easily advance, the artery is probably no longer cannulated.
5. Detach the syringe and connect the catheter to the pressure tubing and functioning irrigation system; an arterial pressure tracing indicates intra-arterial positioning.
6. Secure the catheter line to the skin w/silk ligature; apply sterile dressing and adhesive tape to prevent accidental disconnection.
7. Remove the wrist from its hyperextended position and splint the dorsal aspect to prevent accidental disconnection.

6 CENTRAL VENOUS ACCESS (CVP LINE)

Indications
1. Inadequate peripheral venous access.
2. TPN, use of vasopressor agents that cannot be given through peripheral lines.
3. Chemotherapeutic administration.
4. Central venous and PA pressure monitoring.
5. Frequent blood draws w/difficult IV access.

Anatomy for Central Venous Catheter Placement
1. External jugular vein: formed at the angle of the mandible by the posterior facial veins and the posterior auricular vein; passes caudally over the sternocleidomastoid (SCM) muscle to enter the subclavian vein lateral to the anterior scalene muscle.
2. Internal jugular vein: arises from the base of the skull in the carotid sheath posterior to the internal carotid artery and terminates in the subclavian vein anterior and lateral to the common carotid artery; runs medial to the SCM in its upper part, posterior in triangle between two heads of the SCM and behind the clavicular head in its lower part.

3. Subclavian vein: continuation of axillary vein at the lateral border of the first rib; passes over the first rib anterior to the anterior scalene muscle, continues behind the medial third of the clavicle, where it is fixed to the rib and clavicle; joins the internal jugular to form the innominate vein behind the sternocostoclavicular joint. The subclavian artery and apical pleura lie behind the vein at the medial third of the clavicle.

4. Femoral vein: used as a last resort because of the increased frequency of thrombosis, embolism, and infection. The vein is located medial to the femoral artery in the femoral sheath below the inguinal ligament. The artery may be found at the midpoint of a line connecting the anterior superior iliac spine and the pubic symphysis; the vein is one fingerbreadth medial. A useful mnemonic is NAVEL (Nerve, Artery, Vein, Empty space, Lymphatics).

Principles of Internal Jugular and Subclavian Vein Catheterization

1. Check the INR, APTT, and platelet count before puncture attempts to r/o coagulopathy.

2. Equipment needed: pre-packaged sterile kit that contains apparatus for catheterization by the Seldinger technique. The use of bedside U/S to verify the internal jugular location is increasing and is standard of care in many hospitals.

3. Place a rolled towel vertically between the shoulder blades; put the patient in the Trendelenburg position w/the neck extended. If the patient is anxious and hemodynamically stable, consider sedation.

4. Wear gown, mask, and sterile gloves; prepare and drape the patient.

5. Infiltrate local anesthesia at the puncture site w/25-gauge needle, then a 20-gauge needle; infiltrate track toward the vein, aspirating before instilling anesthetic. It is especially important in subclavian venipuncture to anesthetize the clavicle edge.

6. Flush the catheter w/sterile fluid; estimate the length to the sternomanubrial junction to place in the SVC.

7. Mount an 18-gauge thin-walled needle on the syringe.

8. Insert slowly, while aspirating, until blood returns; advance a few millimeters farther until blood return increases. Bright red blood usually means arterial puncture; remove needle and apply pressure for 10 minutes.

9. If no blood returns, withdraw needle slowly under negative pressure; blood may still return into syringe. If still no blood returns, reattempt.

10. After blood returns, stabilize needle, carefully unscrew syringe, and prevent air embolism by occluding the needle w/a finger.

11. Place a guide wire through the needle gently; it should advance easily. Withdraw the needle, holding the wire in position.

12. Nick the skin w/the #11 blade, slide the dilator over the wire to enlarge the skin site and track, remove the dilator, then advance the catheter over the wire into the desired position.

13. Remove the wire, check blood return on each port and flush it w/NS, and attach IV tubing or caps.

14. Suture at skin and place sterile occlusive dressing.

Specific Sites

1. Internal jugular—central approach
   a. Locate the triangle formed by the two heads of the SCM and the clavicle.
   b. Insert a 22-gauge localizing needle at the apex of the triangle formed by the two heads of the SCM.
   c. Aim the needle parallel to the clavicular head toward the ipsilateral nipple at a 45- to 60-degree angle until the vein is entered. Keep a finger of the nondominant hand on the pulse of the carotid artery to be cognizant of its location.
d. If the needle is inserted 3 cm w/o blood return, attempt a new puncture in a slightly more lateral position.
e. Do not proceed medially because the carotid artery may be punctured.

2. Internal jugular—posterior approach
a. Insert the needle under the SCM three fingerbreadths above the clavicle, aiming anteriorly to the suprasternal notch at a 45-degree angle to the sagittal and horizontal planes.
b. The vein should be entered within 5 to 7 cm of needle penetration.

3. Subclavian vein catheterization (infraclavicular)
a. Insert the needle 1 to 2 cm below the junction of the median and middle thirds of clavicle.
b. Advance the needle parallel to the frontal plane until the clavicle is located.
c. March the needle down the clavicle until it just passes below it, aiming just above the suprasternal notch and keeping the needle parallel to the frontal plane.
d. When the vein is entered, carefully rotate the needle 90 degrees to aim the bevel caudally so that the wire will pass into the innominate vein.

Contraindications
1. Thrombosis of central veins.
2. Coagulopathy: a relative contraindication. Many coagulopathies can be temporarily overcome w/transfusion of FFP, cryoprecipitate, or platelets, followed by immediate venipuncture. It is preferable to place deep lines in areas that are compressible in the event of bleeding (i.e., femoral, brachial, internal jugular). Also consider cutdown of antecubital veins.

Complications
1. Catheter misplacement: poor blood return, cardiac irritability, pain in neck or ear. Corrective options include the following:
a. Reposition under fluoroscopy.
b. Reattempt entire procedure.
2. Arterial puncture (subclavian, carotid, femoral).
3. Hemorrhage: venous or arterial.
4. Pneumothorax: always check CXR after placement and after failed attempts and before reattempting central venipuncture on the contralateral side.
5. Thoracic duct injury with or w/o chylothorax.
6. Extravasation of fluid, hyperalimentation, and so forth.
7. Neural injury (brachial plexus).
8. Air embolism.
9. Catheter or wire embolization.
10. Hydrothorax
   a. Primary: placement of the catheter into pleural or mediastinal spaces.
   b. Secondary: erosion of the catheter through SVC after successful placement.
11. Infection
   a. Cellulitis at puncture site.
   b. Bacteremia from catheter colonization (catheter sepsis).
   c. Increased incidence w/use of multilumen catheters.
12. Thrombosis (central venous): clinical signs include unilateral upper extremity edema, upper extremity and neck venous distention, and neck pain. Treatment: similar to that of iliofemoral DVT. Remove the catheter, heparinize, and follow w/long-term warfarin administration because there is a well-described incidence of PE after subclavian vein thrombosis.

Reference
F. Facts and Formulas

1 CARDIOVASCULAR

See Box 1-4.

2 PULMONARY

See Box 1-5.

3 RENAL FLUIDS, ELECTROLYTES

See Boxes 1-6 and 1-7 and Tables 1-23 and 1-24.

4 CALCIUM

See Box 1-8.

5 NUTRITION

See Box 1-9.

6 EPIDEMIOLOGY

See Box 1-10.

7 MISCELLANEOUS

See Box 1-11.

Box 1-4 • Cardiovascular Formulas

Output of left ventricle 
\[ \text{O}_2 \text{ consumption (mL/min)} = \frac{[\text{CaO}_2 - \text{CvO}_2]}{250 \text{ mL/min}} - \frac{140 \text{ mL/L venous blood in pulmonary artery}}{190 \text{ mL/L arterial blood}} \]

\[ = \frac{250 \text{ mL/min}}{50 \text{ mL/L}} = 5 \text{ L/min} \]

CI = Cardiac output/Body surface area 
Normal = 3.0-3.4 L/min/m²

EF = \( \frac{\text{End-diastolic volume} - \text{end-systolic volume}}{\text{End-diastolic volume}} \) = %

Mean arterial (or pulmonary) pressure = DBP + \( \frac{1}{3}(\text{SBP} - \text{DBP}) \)
Mean pulmonary arterial pressure = DPAP + \( \frac{1}{3}(\text{SPAP} - \text{DPAP}) \)

Pulmonary vascular resistance index (PVRI) = 79.92 \( \frac{\text{mean PAP} - \text{PAOP}}{\text{CI}} \)
Normal = 255-285 dyne-sec/cm²

Shunt % = (Qs/Qt)

\[ \text{Qs/Qt} = \frac{\text{CcO}_2 - \text{CaO}_2}{\text{CcO}_2 - \text{CvO}_2} \]

\[ \text{CcO}_2 = \text{Hgb} \times 1.34 + \text{(alveolar Po}_2 \times 0.003) \]

Normal = <10%
Considerable disease = 20%-29%
Life-threatening = >30%

SV = (end-diastolic volume) - (end-systolic volume)

Systemic vascular resistance index (SVRI) = 79.92 \( \frac{\text{MAP} - \text{CVP}}{\text{CI}} \)

Venous blood \( \text{O}_2 \) content (CvO₂) = \( (\text{PvO}_2 \times 0.003) + (1.34 \times \text{Hgb in g} \times \text{venous blood Hgb } \text{O}_2 \text{ sat %}) \)

Normal = 13-16 mL/dL

Cl, cardiac index; CVP, central venous pressure; DBP, diastolic blood pressure; DPAP, diastolic pulmonary artery pressure; EF, ejection fraction; MAP, mean arterial pressure; PAOP, pulmonary artery occlusion pressure; PAP, pulmonary artery pressure; SBP, systolic blood pressure; SPAP, systolic pulmonary artery pressure; SV, stroke volume.
**Box 1-5 • Pulmonary Formulas**

**Lung volumes.** Normal values for lung volumes in upright subjects:

<table>
<thead>
<tr>
<th>Volume or Capacity</th>
<th>Approximate Value in Upright Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lung capacity (TLC)</td>
<td>6 L</td>
</tr>
<tr>
<td>Vital capacity (VC)</td>
<td>4.5 L</td>
</tr>
<tr>
<td>Residual volume (RV)</td>
<td>1.5 L</td>
</tr>
<tr>
<td>Inspiratory capacity (IC)</td>
<td>3 L</td>
</tr>
<tr>
<td>Functional residual capacity (FRC)</td>
<td>3 L</td>
</tr>
<tr>
<td>Inspiratory reserve volume (IRV)</td>
<td>2.5 L</td>
</tr>
<tr>
<td>Expiratory reserve volume (ERV)</td>
<td>1.5 L</td>
</tr>
<tr>
<td>Tidal volume (V_t)</td>
<td>0.5 L</td>
</tr>
</tbody>
</table>

The VC is calculated as: \[ VC = IRV + ERV + V_t \]

The RV is calculated as the difference between the FRC and the ERV: \[ RV = FRC - ERV \]

Alternatively, if the TLC and VC are known, the following formula can be used: \[ RV = TLC - VC \]

**Alveolar-Arterial Oxygen Gradient (A-a gradient)**

\[
A-a\ gradient = \left[ 713(F_{IO_2}) - \left( \frac{PaCO_2}{0.8} \right) \right] - PaO_2
\]

Normal A-a gradient = 5-15 mm

- F\textsubscript{IO_2}, fraction of inspired oxygen (normal = 0.21-1.0)
- Pa\textsubscript{CO_2}, arterial carbon dioxide tension (normal = 35-45 mm Hg)
- Pa\textsubscript{O_2}, arterial partial pressure of oxygen (normal = 70-100 mm Hg)

**Differential dx of A-a gradient:**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>15% O_2</th>
<th>100% O_2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion defect</td>
<td>Increased gradient</td>
<td>Correction of gradient</td>
</tr>
<tr>
<td>Ventilation-perfusion mismatch</td>
<td>Increased gradient</td>
<td>Partial or complete correction of gradient</td>
</tr>
<tr>
<td>Right-to-left shunt (intracardiac or pulmonary)</td>
<td>Increased gradient</td>
<td>Increased gradient (no correction)</td>
</tr>
</tbody>
</table>
**Box 1-6  Renal Fluids and Electrolytes Formulas**

**Calculation of Creatinine Clearance \( (C_{Cr}) \)**

\[
C_{Cr} \text{ (male)} = \frac{140 - \text{age}}{\text{wt (in kg)}} \times \text{Serum creatinine} \times 72
\]

\[
C_{Cr} \text{ (female)} = 0.85 \times C_{Cr} \text{ (male)}
\]

**Calculation of Fractional Excretion of Sodium \( (FE_{Na}) \)**

\[
FE_{Na} \% = \frac{\text{Quantity of Na}^+ \text{ excreted}}{\text{Quantity of Na}^+ \text{ filtered}} \times 100
\]

or

\[
FE_{Na} \% = \frac{U/P_{Na} \times 100}{U/P_{Cr}}
\]

or

\[
FE_{Na} \% = \frac{U_{Na} \times V}{P_{Na} \times (U_{Cr} \times V/P_{Cr})} \times 100
\]

or

\[
FE_{Na} \% = \frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100
\]

where \( U_{Na} \) is urine sodium concentration, \( V \) is urine flow rate, \( P_{Na} \) is plasma sodium concentration, \( U_{Cr} \) is urine creatinine concentration, and \( P_{Cr} \) is plasma creatinine concentration.

**Sodium Formulas**

**Serum sodium correction in hyperglycemia**

\[
\text{Na}^+ \text{ (euglycemic)} = \text{Measured Na}^+ + 0.028 \times (\text{glucose} - 100)
\]

**Estimated sodium deficit in hyponatremia**

\[
\text{Na}^+ \text{ deficit (mEq)} = 0.6 \times \text{body weight} \times \left( \text{desired plasma Na}^+ - \text{current plasma Na}^+ \right)
\]

**Estimated sodium excess in hypernatremia**

\[
\text{Na}^+ \text{ excess (mEq/L)} = 0.6 \times \text{body weight (kg)} \times \left( \text{current plasma Na}^+ - 140 \right)
\]

Serum sodium correction in hyperlipidemia and hyperproteinemia

- Decrease \( \text{mEq/L} \) serum \( \text{Na}^+ \) in hyperlipidemia = plasma lipids \( \text{mg/dL} \) \times 0.002
- Decrease \( \text{mEq/L} \) serum \( \text{Na}^+ \) in hyperproteinemia = increment of total protein \( > 8 \text{ g/dL} \times 0.25 \)

**Potassium Formulas**

**Diagnostic equations for hyperkalemia:**

- Fractional excretion of potassium \( (FEK) \)

\[
\left( \frac{U_{K}/S_{K}}{U_{Cr}/S_{Cr}} \right) \times 100\%
\]

\[
\text{FEK < 10\%} \text{ indicates renal cause}
\]

\[
\text{FEK > 10\%} \text{ indicates extrarenal cause}
\]

- Transtubular potassium gradient

\[
\frac{[(U_{K}/(U_{osmol}/S_{osmol}))]}{S_{K}}
\]

\[
\text{Gradient < 6-8 indicates renal cause}
\]

\[
\text{Gradient > 6-8 indicates extrarenal cause}
\]

Osmolality Formulas

- Calculated osmolality = \( 2(\text{Na}^+ + K^+) + \frac{\text{Glucose}}{18} + \frac{\text{BUN}}{2.8} \)

- Effective osmolality = \( 2(\text{Na}^+) + \frac{\text{Glucose}}{18} \)

Osmolal gap = Measured osmolality – calculated osmolality

\( U_{K} \), urine potassium; \( S_{K} \), serum potassium; \( U_{Cr} \), urine creatinine; \( S_{Cr} \), serum creatinine; \( U_{osmol} \), urine osmolality; \( S_{osmol} \), serum osmolality.
Box 1-7 • Water Balance

To estimate the amount of total body water (TBW), the following formula is frequently used:

\[ TBW = \text{Body weight (kg)} \times 60\% \]

The water deficit of a patient can be estimated by the following equation:

\[ \text{Water deficit} = 0.6 \times \text{body weight in kg} \times (\frac{\text{P}_{\text{Na}}}{140} - 1) \]

where \( \text{P}_{\text{Na}} \) is plasma sodium concentration.

Alternatively, the free water deficit from the osmolality can be calculated as the following:

\[ \text{H}_2\text{O deficit (L)} = \text{Total body weight (kg)} \times 0.6 \left(1 - \frac{\text{normal osm}}{\text{observed osm}}\right) \]

To calculate the free water clearance based on the osmolar clearance, the following formula can be used:

**Free water clearance** = Urine volume – osmolar clearance

where the osmolar clearance is calculated as:

**Osmolar clearance** = \( \frac{\text{Urine osmolarity} \times \text{urine volume}}{\text{Plasma osmolality}} \)

---

**TABLE 1-23 • Daily Body Fluids**

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Na (mEq/L)</th>
<th>K (mEq/L)</th>
<th>Cl (mEq/L)</th>
<th>HCO₃ (mEq/L)</th>
<th>Volume (mL/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary</td>
<td>145</td>
<td>5</td>
<td>100</td>
<td>35</td>
<td>50-800</td>
</tr>
<tr>
<td>Diarrheal</td>
<td>60</td>
<td>35</td>
<td>40</td>
<td>30</td>
<td>Varies</td>
</tr>
<tr>
<td>Gastric</td>
<td>60</td>
<td>10</td>
<td>130</td>
<td>0</td>
<td>100-4000</td>
</tr>
<tr>
<td>Ileal</td>
<td>130</td>
<td>5</td>
<td>100</td>
<td>50</td>
<td>100-9000</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>140</td>
<td>5</td>
<td>75</td>
<td>115</td>
<td>100-800</td>
</tr>
<tr>
<td>Salivary</td>
<td>10</td>
<td>26</td>
<td>10</td>
<td>30</td>
<td>500-2000</td>
</tr>
</tbody>
</table>

---

**TABLE 1-24 • Replacement Fluids**

<table>
<thead>
<tr>
<th>Fluids</th>
<th>Na (mEq/L)</th>
<th>K (mEq/L)</th>
<th>Cl (mEq/L)</th>
<th>HCO₃ (mEq/L)</th>
<th>Ca (mEq/L)</th>
<th>Kcal/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{1}{2} ) Normal saline</td>
<td>77</td>
<td>—</td>
<td>77</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Normal saline</td>
<td>154</td>
<td>—</td>
<td>154</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>D₅W</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>170</td>
</tr>
<tr>
<td>D₁₀W</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>340</td>
</tr>
<tr>
<td>Lactated Ringer’s solution</td>
<td>130</td>
<td>4</td>
<td>109</td>
<td>28*</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Extracellular fluid</td>
<td>141</td>
<td>4</td>
<td>—</td>
<td>27</td>
<td>5</td>
<td>—</td>
</tr>
</tbody>
</table>

*Lactate converted to HCO₃ in liver.*
**Box 1-8 • Calcium Formulas**

The correction of Ca based on the serum albumin and globulin levels is calculated as:

\[
\text{% Ca bound} = 8(\text{albumin}) + 2(\text{globulin}) + 3
\]

Another formula to correct \( C_{\text{Ca}} \) based on total protein is:

\[
\text{Corrected Ca} = \frac{\text{Measured Ca}}{0.6 + (\text{total protein}/8.5)}
\]

A quick bedside formula for calculation of the corrected Ca is:

\[
\text{Corrected Ca} = \text{Measured Ca} - \text{albumin} + 4
\]

**Box 1-9 • Nutrition Formulas**

Basal energy expenditure (BEE) can be determined by the Harris-Benedict formulas:

\[
\begin{align*}
\text{BEE male} &= 66.5 + [13.7 \times \text{wt (in kg)}] + [5 \times \text{ht (in cm)}] - [6.8 \times \text{age (in yr)}] \\
\text{BEE female} &= 655 + [9.6 \times \text{wt (in kg)}] + [1.8 \times \text{ht (in cm)}] - [4.7 \times \text{age (in yr)}]
\end{align*}
\]

For states other than basal, the BEE is multiplied by a correction factor:

- Low stress: 1.3 \times \text{BEE}
- Moderate stress: 1.5 \times \text{BEE}
- Cancer: 1.6 \times \text{BEE}
- Sepsis (normotensive): 1.7 \times \text{BEE}
- Severe stress: 2 \times \text{BEE}
- Severe burn (>40% of body surface area, normotensive patient): 2.5 \times \text{BEE}

**Box 1-10 • Epidemiology Formulas**

<table>
<thead>
<tr>
<th>Sensitivity, Specificity</th>
<th>dz +</th>
<th>dz –</th>
</tr>
</thead>
<tbody>
<tr>
<td>test +</td>
<td>a</td>
<td>b</td>
</tr>
<tr>
<td>test –</td>
<td>c</td>
<td>d</td>
</tr>
</tbody>
</table>

Sensitivity = \( \frac{a}{a + c} \) (screening test)
Specificity = \( \frac{d}{b + d} \) (confirming test)

Positive predictive value = \( \frac{a}{a + b} \) (influenced by prevalence)
Negative predictive value = \( \frac{d}{b + d} \) (influenced by prevalence)

**Odds Ratio, Relative Risk**

<table>
<thead>
<tr>
<th>dz +</th>
<th>dz –</th>
</tr>
</thead>
<tbody>
<tr>
<td>exposure +</td>
<td>a</td>
</tr>
<tr>
<td>exposure –</td>
<td>c</td>
</tr>
</tbody>
</table>

**Box 1-11 • Miscellaneous Formulas**

Parkland formula = 4 mL/kg \times \% burn
→ fluid given during 24 hr:
Administer \( \frac{1}{2} \) of total in first 8 hr
Administer \( \frac{1}{2} \) of total during next 16 hr

Volume of distribution = amount drug in body/plasma drug concentration
Weight conversion: \( \text{lb} = \text{kg} \times 2.2 \)
Temperature conversion: \( ^{\circ}C = (^{\circ}F - 32)(5/9) \)

G. Formulary

1. **IV DRIPS**

See Table 1-25.

2. **STEROID CONVERSION TABLE**

See Table 1-26.

3. **REGULAR INSULIN (SC) SLIDING SCALE**

See Table 1-27.
<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Indication</th>
<th>Comments and Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vasopressors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td>1-20 µg/kg/min</td>
<td>Cardiogenic, septic shock; low dose can preserve renal blood flow and promote urinary output</td>
<td>May cause tachyarrhythmias, ischemic limb necrosis</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>10-200 µg/min</td>
<td>Hypotension</td>
<td>Pure α agonist</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>1-20 µg/min</td>
<td>Septic shock w/hypotension refractory to dopa (low systemic vascular resistance and adequately resuscitated)</td>
<td>Potent α agonist (vasoconstrictor); avoid in cardiogenic shock</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>0.01-0.04 unit/min</td>
<td>Refractory vasodilatory shock (late)</td>
<td>Avoid w/CAD</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>2-20 µg/kg/min</td>
<td>Severe systolic heart failure</td>
<td>Inotrope and systemic vasodilator</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>1-20 µg/min or 30-100 ng/kg/min</td>
<td>Second line for cardiogenic shock</td>
<td>Chronotrope, inotrope, and vasoconstrictor</td>
</tr>
<tr>
<td><strong>Antihypertensives</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>0.5-5 µg/kg/min</td>
<td>Severe HTN (particularly w/low CO)</td>
<td>Potent vasodilator; caution in renal and hepatic failure (cyanide/thiocyanide toxicity); do not use alone in dissection (reflex tachycardia); can ↓ Pao2 due to pulmonary shunting</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>10-400 µg/min</td>
<td>Augment CO (intermediate dose), angina (low dose, typically 0.5-0.6 mg SL q5min); hypertensive crisis</td>
<td>Predominantly venodilator, mediated by nitric oxide; rapid onset; headache; ↑ ICP; methemoglobinemia; tachyphylaxis</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>5-15 mg/hr</td>
<td>HTN, ↓ cerebral vasospasm</td>
<td>Potent CCB, vasodilator; renal clearance</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>5-15 mg/hr</td>
<td>HTN, atrial fibrillation</td>
<td>CCB, monitor HR and BP, especially if also on β-blocker</td>
</tr>
<tr>
<td>Esmolol</td>
<td>50-300 µg/kg/min</td>
<td>HTN, particularly w/aortic dissection; supraventricular tachycardia</td>
<td>β₁-Blocker, short acting</td>
</tr>
<tr>
<td><strong>Paralytics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vecuronium</td>
<td>0.05-0.1 mg/kg/hr</td>
<td>Paralysis</td>
<td>Monitor muscle twitch (2/4 train-of-four); nondepolarizing; onset 1-2 min; caution w/hepatic failure; caution w/steroids (including myopathy)</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>0.5-10 µg/kg/min</td>
<td>Paralysis w/renal or hepatic failure</td>
<td>Nondepolarizing, Hoffman elimination</td>
</tr>
<tr>
<td><strong>Sedative</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>1-10 mg/hr</td>
<td>Sedation</td>
<td>Potent, short acting but can result in accumulation</td>
</tr>
</tbody>
</table>
TABLE 1-26 Steroid Conversion Scale

<table>
<thead>
<tr>
<th>Corticosteroids</th>
<th>Approximate Equivalent Dose (mg)</th>
<th>Relative Anti-inflammatory Potency</th>
<th>Relative Mineralocorticoid Potency</th>
<th>Biologic Half-life (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>0.6-0.75</td>
<td>20-30</td>
<td>0</td>
<td>36-54</td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
<td>2</td>
<td>8-12</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>20-30</td>
<td>0</td>
<td>36-54</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>2</td>
<td>8-12</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>18-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>18-36</td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>18-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>18-36</td>
</tr>
</tbody>
</table>

TABLE 1-27 Regular Insulin (SC) Sliding Scale

<table>
<thead>
<tr>
<th>Finger Stick Blood Glucose</th>
<th>Mild Scale</th>
<th>Moderate Scale</th>
<th>Aggressive Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>1 amp (25 g) D50 or orange juice, call MD</td>
<td>1 amp D50 or orange juice, call MD</td>
<td>1 amp D50 or orange juice, call MD</td>
</tr>
<tr>
<td>60-150</td>
<td>No insulin</td>
<td>No insulin</td>
<td>No insulin</td>
</tr>
<tr>
<td>151-200</td>
<td>No insulin</td>
<td>3 units</td>
<td>4 units</td>
</tr>
<tr>
<td>201-250</td>
<td>2 units</td>
<td>5 units</td>
<td>6 units</td>
</tr>
<tr>
<td>251-300</td>
<td>4 units</td>
<td>7 units</td>
<td>10 units</td>
</tr>
<tr>
<td>301-350</td>
<td>6 units</td>
<td>9 units</td>
<td>12 units</td>
</tr>
<tr>
<td>351-400</td>
<td>8 units</td>
<td>11 units</td>
<td>15 units</td>
</tr>
<tr>
<td>&gt;400</td>
<td>10 units, call physician</td>
<td>13 units, call physician</td>
<td>18 units, call physician</td>
</tr>
</tbody>
</table>

4 OPIOID ANALGESICS DOSING TABLE

See Table 1-28.

5 HEPARIN SLIDING SCALE

See Box 1-12.

6 NUTRITION FEEDS

See Table 1-29.

7 THERAPY FOR COMMON SIDE EFFECTS

Nausea/Vomiting
- Metoclopramide (Reglan): 10-20 mg IV/PO q3-6h.
- Promethazine (Phenergan): 12.5-25 mg IV/PO/PR q4-6h.
- Droperidol: 0.625 mg IV q4-6h.
- Ondansetron (Zofran): 4-8 mg IV q4h.

Constipation
- Docusate sodium: 250 mg PO bid.
- MOM: 30 mL PO bid.
- Lactulose: 30 mL PO bid.
- Senokot: 1-4 tabs PO qd.
- Bisacodyl (Dulcolax): 5-10 mg PO or 10 mg PR qd.
- Fleets enema PRN.
- Magnesium citrate: 300 mL PO PRN.

Sedation
- Decrease dose.
- Add adjuvant.
- Change routes to minimize dose (IV to epidural).
- Change opiates.
- Adjust dosing schedule to normalize sleep-wake cycle.
- Avoid drugs w/sedating effects.

(text continues on page 91)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Ranges in Adults</th>
<th>Duration</th>
<th>Equianalgesic Dose to Morphine 10 mg IV</th>
<th>Patient-Controlled Analgesia Starting Doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Potent Opioids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine [Roxanol</td>
<td>Xanodyne Pharmaceuticals, Inc., Newport, KY], MS Contin [Purdue Pharmaceuticals, Stamford, CT)]</td>
<td>IM, IV, SC 2.5-20 mg q2-6h infusion: 0.5-10 mg/hr Oral prompt release: 10-30 mg q4h Oral extended release: 15-30 mg q8-12h Rectal suppository: 5-10 mg q4-6h</td>
<td>Parenteral: 3-5 hr Oral prompt release: 4 hr Oral extended release: 8-12 hr</td>
<td>Parenteral: 10 mg Oral: 30 mg</td>
<td>Basal: 1-2 mg/hr PCA: 2 mg q10min Range: 0.5-3 mg q10-20min</td>
</tr>
<tr>
<td>Fentanyl [Sublimaze</td>
<td>Janssen-Cilag, High Wycombe, UK], Duragesic [Ortho-McNeil Pharmaceutical, Raritan, NJ)]</td>
<td>IM, IV, SC 50-100 µg q30-60min Transdermal dose as µg/hr</td>
<td>Parenteral: 0.5-1 hr</td>
<td>Parenteral: 100 µg</td>
<td>Basal: 10 µg/hr PCA: 10 µg q10min Range: 10-50 µg q10min</td>
</tr>
<tr>
<td>Hydromorphone [Dilaudid</td>
<td>Abbott Laboratories, Abbott Park, IL)]</td>
<td>IM, IV, SC 1-2 mg q4-6h Oral: 2-4 mg q4-6h Rectal suppository: 6 mg q4-6h</td>
<td>Parenteral: 3-4 hr Oral: 4-6 hr</td>
<td>Parenteral: 2 mg Oral: 4 mg</td>
<td>Basal: 0.2 mg/hr PCA: 0.2 mg q10min Range: 0.1-0.5 mg q10-15min</td>
</tr>
<tr>
<td>Meperidine [Demerol</td>
<td>Sanofi-Aventis, Bridgewater, NJ)]</td>
<td>IM, IV 25-150 mg q3-4h</td>
<td>Parenteral: 2-4 hr Oral: 3-6 hr</td>
<td>Parenteral: 75 mg Oral: 300 mg</td>
<td></td>
</tr>
</tbody>
</table>
### COMMON SIDE EFFECTS

**Perioperative Use of Analgesics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Parenteral Dose</th>
<th>Oral Dose</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone (Dolophine [Roxane Laboratories, Inc., Columbus, OH])</td>
<td>IM, IV, PO</td>
<td>2.5-150 mg q6h</td>
<td>Parenteral: 4-8 hr, Oral: 4-12 hr</td>
<td>Parenteral: 5-10 mg, Oral: 5-10 mg</td>
<td>Methadone has variable half-life, slow titration advised</td>
</tr>
<tr>
<td>Oxycodone (Percocet [Endo Pharmaceuticals, Chadds Ford, PA], Tylox [Ortho-McNeil Pharmaceutical, Raritan, NJ], OxyContin [Purdue Pharmaceuticals, Stamford, CT])</td>
<td>Oral prompt release: 5-10 mg q3-4h, Oral extended release: 10 mg q12h</td>
<td>Oral: 4-5 hr, Oral: 15-30 mg</td>
<td>Note cumulative acetaminophen dosage, adjust acetaminophen dose for liver impairment &lt;2 g/24 hr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Weak Opioids

| Codeine (Tylenol #3 [Ortho-McNeil Pharmaceutical, Raritan, NJ]) | IM, PO | 15-60 mg q4-6h Max. 360 mg/24 hr | Parenteral: 4-6 hr, Oral: 4-6 hr | Parenteral: 120 mg, Oral: 200 mg | Note cumulative acetaminophen dosage, adjust acetaminophen dose for liver impairment <2 g/24 hr |
| Hydrocodone (Vicodin [Abbott Laboratories, Abbott Park, IL], Lortab [UCB Pharmaceuticals Inc., Atlanta, GA]) | PO | 5-10 mg q4-6h | Oral: 4-5 hr, Oral: 40 mg | Note cumulative acetaminophen dosage, adjust acetaminophen dose for liver impairment <2 g/24 hr |

#### Ultra-weak Opioid

| Propoxyphene (Darvon, Darvocet N 100 [Xanodyne Pharmaceuticals, Inc., Newport, KY]) | PO | HCL 65 mg q4h Max. 390 mg/24 hr Napsylate 100 mg q4h, max 600 mg/24 hr | Oral: 4-6 hr | 260 mg as HCL 400 mg as napsylate | Potential for hepatotoxicity, note cumulative acetaminophen dosage, adjust acetaminophen dose for liver impairment <2 g/24 hr |

#### Miscellaneous

| Tramadol (Ultram [Ortho-McNeil Pharmaceutical, Raritan, NJ]) | PO | 50-100 mg q4-6h Max. 400 mg/24 hr | Oral: 4-6 hr | Oral: 300 mg | Seizure risk >400 mg/24 hr, reduce dose in elderly, cirrhosis = 50 mg q12h |
### TABLE 1-29  Nutrition Feeds

<table>
<thead>
<tr>
<th>Product</th>
<th>Energy</th>
<th>Protein</th>
<th>Fat</th>
<th>Carbohydrate</th>
<th>Ca (mg/L)</th>
<th>Phosphate (mg/L)</th>
<th>Na</th>
<th>K</th>
<th>Osm</th>
<th>Vol</th>
<th>% Free</th>
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</thead>
<tbody>
<tr>
<td><strong>Oral Supplements: Intact Protein, Lactose Free</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Resource</td>
<td>1.06</td>
<td>38</td>
<td>0</td>
<td>230</td>
<td>42</td>
<td>680</td>
<td>&lt;338</td>
<td>&lt;84</td>
<td>750</td>
<td>N/A</td>
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<tr>
<td>Boost</td>
<td>1.01</td>
<td>43</td>
<td>18</td>
<td>170</td>
<td>1270</td>
<td>1060</td>
<td>550</td>
<td>1690</td>
<td>640</td>
<td>1180</td>
<td>84</td>
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<tr>
<td>Boost Plus</td>
<td>1.52</td>
<td>61</td>
<td>57</td>
<td>190</td>
<td>850</td>
<td>850</td>
<td>850</td>
<td>1480</td>
<td>670</td>
<td>1180</td>
<td>78</td>
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<tr>
<td>Choice DM</td>
<td>0.93</td>
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<td>43</td>
<td>101</td>
<td>1390</td>
<td>1310</td>
<td>850</td>
<td>1820</td>
<td>400</td>
<td>1310</td>
<td>85</td>
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<tr>
<td><strong>Tube Feeding: Intact Protein, Lactose Free</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Isocal</td>
<td>1.06</td>
<td>34</td>
<td>44</td>
<td>135</td>
<td>630</td>
<td>530</td>
<td>530</td>
<td>1320</td>
<td>270</td>
<td>1890</td>
<td>84</td>
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<tr>
<td>Ultracal HN Plus</td>
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<td>54</td>
<td>40</td>
<td>156</td>
<td>1000</td>
<td>1000</td>
<td>1350</td>
<td>1850</td>
<td>370</td>
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<td>45</td>
<td>124</td>
<td>850</td>
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<td>950</td>
<td>1610</td>
<td>270</td>
<td>1180</td>
<td>85</td>
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<tr>
<td>Deliver 2.0</td>
<td>2.0</td>
<td>75</td>
<td>102</td>
<td>200</td>
<td>1010</td>
<td>1010</td>
<td>800</td>
<td>1680</td>
<td>640</td>
<td>1000</td>
<td>71</td>
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<td><strong>Elemental/Peptide</strong></td>
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<td></td>
<td></td>
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<td>Vivonex TEN</td>
<td>1.0</td>
<td>38</td>
<td>2.8</td>
<td>210</td>
<td>500</td>
<td>500</td>
<td>600</td>
<td>950</td>
<td>630</td>
<td>2000</td>
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<td>40</td>
<td>39</td>
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<td>800</td>
<td>700</td>
<td>560</td>
<td>1500</td>
<td>270</td>
<td>1500</td>
<td>85</td>
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<td><strong>Special Formulations</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Respalor</td>
<td>1.5</td>
<td>75</td>
<td>68</td>
<td>146</td>
<td>1000</td>
<td>1000</td>
<td>1270</td>
<td>1480</td>
<td>400</td>
<td>1000</td>
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<td>Impact</td>
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<td>43</td>
<td>150</td>
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<td>1200</td>
<td>1800</td>
<td>630</td>
<td>1000</td>
<td>78</td>
</tr>
<tr>
<td>Magnacal Renal</td>
<td>2.0</td>
<td>75</td>
<td>101</td>
<td>200</td>
<td>1010</td>
<td>800</td>
<td>800</td>
<td>1270</td>
<td>570</td>
<td>1000</td>
<td>71</td>
</tr>
<tr>
<td>Suplena</td>
<td>2.0</td>
<td>30</td>
<td>96</td>
<td>255</td>
<td>1430</td>
<td>730</td>
<td>790</td>
<td>1120</td>
<td>600</td>
<td>947</td>
<td>71.2</td>
</tr>
</tbody>
</table>
Chapter 1  Surviving the Wards

Box 1-12 • Heparin Dosage Regimens

1. Weight-Based Nomogram
The initial dose is a bolus of 80 U/kg body weight, followed by an infusion starting at a rate of 18 U/kg/hr. The APTT is measured every 6 hr, and the heparin dose is adjusted as follows.

<table>
<thead>
<tr>
<th>Measured Value</th>
<th>Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT &lt;35 sec (&lt;1.2 × control value)</td>
<td>80 U/kg as bolus, then ↑ infusion rate by 4 U/kg/hr</td>
</tr>
<tr>
<td>APTT 35-45 sec (1.2-1.5 × control value)</td>
<td>40 U/kg as bolus, then ↑ infusion rate by 2 U/kg/hr</td>
</tr>
<tr>
<td>APTT 46-70 sec (&gt;1.5-2.3 × control value)</td>
<td>No change</td>
</tr>
<tr>
<td>APTT 71-90 sec (&gt;2.3-3 × control value)</td>
<td>↓ Infusion rate by 2 U/kg/hr</td>
</tr>
<tr>
<td>APTT &gt;90 sec (&gt;3 × control value)</td>
<td>Stop infusion for 1 hr, then ↓ infusion rate by 3 U/kg/hr</td>
</tr>
</tbody>
</table>

2. 5000-U Bolus Dose, Followed by 1280 U/hr

<table>
<thead>
<tr>
<th>APTT (sec)</th>
<th>Bolus (U)</th>
<th>Stop Infusion (min)</th>
<th>Rate of Change (mL/hr)</th>
<th>Repeat APTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50*</td>
<td>5000</td>
<td>0</td>
<td>+3</td>
<td>In 6 hr</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>+3</td>
<td>In 6 hr</td>
</tr>
<tr>
<td>60-85</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Next morning</td>
</tr>
<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>−2</td>
<td>Next morning</td>
</tr>
<tr>
<td>96-120</td>
<td>30</td>
<td>0</td>
<td>−2</td>
<td>In 6 hr</td>
</tr>
<tr>
<td>&gt;120</td>
<td>60</td>
<td>−4</td>
<td></td>
<td>In 6 hr</td>
</tr>
</tbody>
</table>

3. Intravenous Dose-Titration Nomogram for APTT
The starting dose is a 5000-U bolus, followed by 40,000 U/24 hr (if the patient has a low risk of bleeding) or 30,000 U/24 hr (if there is a high risk of bleeding).

<table>
<thead>
<tr>
<th>APTT (sec)</th>
<th>Rate of Change (mL/hr)</th>
<th>Change in Dose (U/24 hr)</th>
<th>Additional Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤45</td>
<td>+6</td>
<td>+5760</td>
<td>Repeat APTT in 4-6 hr</td>
</tr>
<tr>
<td>46-54</td>
<td>+3</td>
<td>+2880</td>
<td>Repeat APTT in 4-6 hr</td>
</tr>
<tr>
<td>55-85</td>
<td>0</td>
<td>0</td>
<td>None*</td>
</tr>
<tr>
<td>86-110</td>
<td>−3</td>
<td>−2880</td>
<td>Stop heparin for 1 hr; repeat APTT 4-6 hr after restarting heparin Rx</td>
</tr>
<tr>
<td>&gt;110</td>
<td>−6</td>
<td>−5760</td>
<td>Stop heparin for 1 hr; repeat APTT 4-6 hr after restarting heparin Rx</td>
</tr>
</tbody>
</table>

*If the APTT is subtherapeutic despite a heparin dose of at least 1440 U/hr (36 mL/hr) at any time during the first 48 hours of therapy, the response to an APTT of <50 sec is a bolus of 5000 U and a rate increase of 5 mL/hr.

A heparin sodium concentration of 20,000 U in 500 mL is equal to 40 U/mL.

During the first 24 hours, repeat the APTT in 4 to 6 hours. Thereafter, the APTT is determined once daily, unless the value is in the therapeutic range.

Note: 1 mL/hr = 40 U/hr.

Pruritus
- Diphenhydramine (Benadryl): 10-25 mg IV/PO q4-6h.
- Hydroxyzine (Atarax, Vistaril): 25 mg PO/IM q6h.
- Nalbuphine (Nubain): 2.5-5 mg IV q2-4h.

Key Concepts
- Administer on scheduled basis.
- Provide PRN for breakthrough pain.
- Consider adjuvants (NSAIDs, antidepressant sleep agents, anesthetics).

Reference
H. DVT Prophylaxis

1. Risk score for venous thromboembolism in hospitalized pts is shown in Table 1-30 (high risk is ≥4).

2. Options for thromboprophylaxis in hospitalized medical pts:
   a. Unfractionated heparin: (UFH) 5000 U SC tid
   b. Enoxaparin: 40 mg SC qd
   c. Dalteparin: starting dose is 100 to 200 U/kg, then 5000 U SC qd
   d. Fondaparinux: 2.5 mg SC qd
   e. Graduated compression stockings or pneumatic compression device (for pts w/contraindications to anticoagulation)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>3</td>
</tr>
<tr>
<td>Prior venous thromboembolism</td>
<td>3</td>
</tr>
<tr>
<td>Hypercoagulability</td>
<td>3</td>
</tr>
<tr>
<td>Major surgery</td>
<td>2</td>
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<tr>
<td>Advanced age</td>
<td>1</td>
</tr>
<tr>
<td>Obesity</td>
<td>1</td>
</tr>
<tr>
<td>Bed rest</td>
<td>1</td>
</tr>
<tr>
<td>Use of hormone replacement therapy or oral contraceptives</td>
<td>1</td>
</tr>
</tbody>
</table>

References

American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE).

I. ACLS ALGORITHMS

1 PULSELESS ARREST
See Figure 1-15.

2 BRADYCARDIA
See Figure 1-16.

3 TACHYCARDIA
See Figure 1-17.
PULSELESS ARREST

• BLS Algorithm: Call for help, give CPR
• Give oxygen when available
• Attach monitor/defibrillator when available

VF/VT

Check rhythm

Shockable rhythm?

Not shockable

Give 1 shock
• Manual biphasic: device specific (typically 120 to 200 J) Note: If unknown use 200 J
• AED: device specific
• Monophasic: 360 J
Resume CPR immediately

Give 5 cycles of CPR*

Check rhythm

Shockable rhythm?

No

Resume CPR immediately after the shock
When IV/I/O available, give vasopressor during CPR (before or after the shock)
• Epinephrine 1 mg IV/I/O
Repeat every 3 to 5 min
or
• May give 1 dose of vasopressin 40 U IV/I/O to replace first or second dose of epinephrine

Give 5 cycles of CPR*

If asystole, go to Box 10
• If electrical activity, check pulse. If no pulse, go to Box 10
• If pulse present, begin postresuscitation care

Asystole/PEA

Resume CPR immediately for 5 cycles
When IV/I/O available, give vasopressor
• Epinephrine 1 mg IV/I/O
Repeat every 3 to 5 min
or
• May give 1 dose of vasopressin 40 U IV/I/O to replace first or second dose of epinephrine

Consider atropine 1 mg IV/I/O for asystole or slow PEA rate. Repeat every 3 to 5 min (up to 3 doses)

Check rhythm

Shockable rhythm?

Not shockable

Check rhythm

Shockable

Give 5 cycles of CPR*

Continue CPR while defibrillator is charging
Give 1 shock
• Manual biphasic: device specific (same as first shock or higher dose) Note: If unknown, use 200 J
• AED: device specific
• Monophasic: 360 J
Resume CPR immediately after the shock
When IV/I/O available, give vasopressor during CPR (before or after the shock)
• Epinephrine 1 mg IV/I/O
Repeat every 3 to 5 min
or
• May give 1 dose of vasopressin 40 U IV/I/O to replace first or second dose of epinephrine

Give 5 cycles of CPR*

If asystole, go to Box 10
• If electrical activity, check pulse. If no pulse, go to Box 10
• If pulse present, begin postresuscitation care

Continue CPR while defibrillator is charging
Give 1 shock
• Manual biphasic: device specific (same as first shock or higher dose) Note: If unknown, use 200 J
• AED: device specific
• Monophasic: 360 J
Resume CPR immediately after the shock
Consider antiarrhythmics; give during CPR (before or after the shock)
amiodarone (300 mg IV/I/O once, then consider additional 150 mg IV/I/O once) or lidocaine (1 to 1.5 mg/kg first dose, then 0.5 to 0.75 mg/kg IV/I/O, maximum 3 doses or 3 mg/kg)
Consider magnesium, loading dose 1 to 2 g IV/I/O for torsades de pointes
After 5 cycles of CPR, * go to Box 5 above

During CPR

• Push hard and fast (100/min)
• Ensure full chest recoil
• Minimize interruptions in chest compressions
• One cycle of CPR: 30 compressions then 2 breaths; 5 cycles = 2 min
• Avoid hyperventilation
• Secure airway and confirm placement
• After an advanced airway is placed, rescuers no longer deliver “cycles” of CPR. Give continuous chest compressions without pauses for breaths. Give 8 to 10 breaths/minute. Check rhythm every 2 minutes
• Rotate compressors every 2 minutes with rhythm checks
• Search for and treat possible contributing factors:
  - Hypovolemia
  - Hypoxia
  - Hydrogen ion (acidosis)
  - Hypo-/hyperkalemia
  - Hypoglycemia
  - Hypothermia
  - Toxins
  - Tamponade, cardiac
  - Tension pneumothorax
  - Thrombosis (coronary or pulmonary)
  - Trauma

BRADYCARDIA
Heart rate < 60 bpm and inadequate for clinical condition

2
• Maintain patient airway; assist breathing as needed
• Give oxygen
• Monitor ECG (identify rhythm), blood pressure, oximetry
• Establish IV access

3
Signs or symptoms of poor perfusion caused by the bradycardia?
(e.g. acute altered mental status, ongoing chest pain, hypotension or other signs of shock)

4A
Observe/Monitor

Reminders
• If pulseless arrest develops, go to Pulseless Arrest Algorithm
• Search for and treat possible contributing factors:
  - Hypovolemia
  - Hypoxia
  - Hydrogen ion (acidosis)
  - Hypo-/hyperkalemia
  - Hypoglycemia
  - Hypothermia
  - Toxins
  - Tamponade, cardiac
  - Thrombosis (coronary or pulmonary)
  - Trauma (hypovolemia, increased ICP)

4
Adequate perfusion
Poor perfusion

• Prepare for transcutaneous pacing; use without delay for high-degree block (type II second-degree block or third-degree AV block)
• Consider atropine 0.5 mg IV while awaiting pacer. May repeat to a total dose of 3 mg. If ineffective, begin pacing
• Consider epinephrine (2 to 10 μg/min) or dopamine (2 to 10 μg/kg per min) infusion while awaiting pacer or if pacing ineffective

5
• Prepare for transvenous pacing
• Treat contributing causes
• Consider expert consultation

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FIGURE 1-16. Bradycardia algorithm.
TACHYCARDIA

With pulses

1. Assess and support ABCs as needed
2. Give oxygen
3. Monitor ECG (identify rhythm), blood pressure, oximetry
4. Identify and treat reversible causes

With pulses

5. Establish IV access
6. Obtain 12-lead ECG (when available) or rhythm strip
7. Is QRS narrow (< 0.12 sec)?

Narrow

Irregular Narrow-Complex
Tachycardia
Probable atrial fibrillation or possible atrial flutter or MAT (multifocal atrial tachycardia)
- Consider expert consultation
- Control rate (eg. diltiazem, β-blockers; use β-blockers with caution in pulmonary disease or CHF)

8. Attempt vagal maneuvers
- Give adenosine 6 mg rapid IV push. If no conversion, give 12 mg rapid IV push; may repeat 12 mg dose once

9. Does rhythm convert?
- Note: Consider expert consultation

If rhythm converts, probable reentry SVT (reentry supraventricular tachycardia):
- Observe for recurrence
- Treat recurrence with adenosine or longer-acting AV nodal blocking agents (eg. diltiazem, β-blockers)

If rhythm does NOT convert, possible atrial flutter, ectopic atrial tachycardia, or junctional tachycardia:
- Control rate (eg. diltiazem, β-blockers; use β-blockers with caution in pulmonary disease or CHF)
- Treat underlying cause
- Consider expert consultation

10. Treat possible contributing factors:
- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo-hyperkalemia
- Hypoglycemia
- Hypothermia

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FIGURE 1-17. Tachycardia algorithm.
The Differential Diagnosis: Zebras or Horses?

Pearls of wisdom
Common things occur commonly.
When you hear hoofbeats, think of horses, not zebras.
Place your bets on uncommon manifestations of common conditions rather than common manifestations of uncommon conditions.

1 ABDOMINAL DISTENTION

Nonmechanical Obstruction
Excessive intraluminal gas
Intra-abdominal infection
Trauma
Retroperitoneal irritation (renal colic, neoplasms, infections, hemorrhage, ruptured AAA)
Vascular insufficiency (thrombosis, embolism)
Mechanical ventilation
Extra-abdominal infection (sepsis, pneumonia, empyema, osteomyelitis of spine)
Metabolic/toxic abnormalities (hypokalemia, uremia, lead poisoning)
Chemical irritation (perforated ulcer, bile, pancreatitis)
Peritoneal inflammation
Severe pain, pain medications
Pseudo-obstruction in the elderly (Ogilvie syndrome)

Mechanical Obstruction
Neoplasm (intraluminal, extraluminal)
Adhesions, endometriosis
Infection (intra-abdominal abscess, diverticulitis)
Gallstones
Foreign body, bezoars
Pregnancy

Hernias
Volvulus
Stenosis at surgical anastomosis, radiation stenosis
Fecaliths
IBD
Gastric outlet obstruction
Hematoma
Other: parasites, superior mesenteric artery syndrome, pneumatosis intestinalis, annular pancreas, Hirschspring’s disease, intussusception, meconium

2 ABDOMINAL PAIN

Diffuse
Early appendicitis
Aortic aneurysm
Gastroenteritis (crampy pain)
Intestinal obstruction
Diverticulitis
Peritonitis
Mesenteric insufficiency or infarction
Pancreatitis
IBD
Irritable bowel
Mesenteric adenitis
Metabolic: toxins, lead poisoning, uremia, drug OD, DKA, heavy metal poisoning
Sickle cell crisis
Pneumonia (rare)
Trauma
UTI, PID
Chapter 2  The Differential Diagnosis: Zebras or Horses?

Other: narcotic withdrawal, acute intermittent porphyria, tabes dorsalis, PAN, Henoch-Schönlein purpura, adrenal insufficiency

**Epigastric**
- Gastric: PUD, gastric outlet obstruction, gastric ulcer
- Duodenal: PUD, duodenitis
- Biliary: cholecystitis, cholangitis
- Hepatic: hepatitis
- Pancreatic: pancreatitis
- Intestinal: high small bowel obstruction, early appendicitis
- Cardiac: angina, MI, pericarditis
- Pulmonary: pneumonia, pleurisy, pneumothorax
- Subphrenic abscess
- Vascular: dissecting aneurysm, mesenteric ischemia

**Suprapubic**
- Intestinal: colon obstruction or gangrene, diverticulitis, appendicitis
- Reproductive system: ectopic pregnancy, mittelschmerz, torsion of ovarian cyst, PID, salpingitis, endometriosis, rupture of endometrioma
- Urinary system: cystitis, rupture of urinary bladder; bladder distention/urinary outlet obstruction

**Right Upper Quadrant**
- Biliary: calculi, infection, inflammation, neoplasm
- Hepatic: hepatitis, abscess, hepatic congestion, neoplasm, trauma
- Gastric: PUD, pyloric stenosis, neoplasm, alcoholic gastritis, hiatal hernia
- Pancreatic: pancreatitis, neoplasm, stone in pancreatic duct or ampulla
- Renal: calculi, infection, inflammation, neoplasm, rupture of kidney
- Pulmonary: pneumonia (RLL), pulmonary infarction, right-sided pleurisy
- Intestinal: retrocecal appendicitis, intestinal obstruction, high fecal impaction, diverticulitis
- Cardiac: myocardial ischemia (particularly involving the inferior wall), pericarditis
- Cutaneous: herpes zoster
- Trauma
- Fitz-Hugh–Curtis syndrome (perihepatitis)
- Hepatic flexure syndrome

**Left Upper Quadrant**
- Gastric: PUD, gastritis, pyloric stenosis, hiatal hernia
- Pancreatic: pancreatitis, neoplasm, stone in pancreatic duct or ampulla
- Cardiac: MI, angina pectoris
- Splenic: splenomegaly, ruptured spleen, splenic abscess, splenic infarction
- Renal: calculi, pyelonephritis, neoplasm
- Pulmonary: pneumonia, empyema, pulmonary infarction
- Vascular: ruptured aortic aneurysm
- Cutaneous: herpes zoster
- Trauma
- Intestinal: high fecal impaction, perforated colon, diverticulitis
- Splenic flexure syndrome

**Periumbilical**
- Intestinal: small bowel obstruction or gangrene, early appendicitis
- Vascular: mesenteric thrombosis, dissecting aortic aneurysm
- Pancreatic: pancreatitis
- Metabolic: uremia, DKA
- Umbilical hernia—incarcerated
- Trauma

**Right Lower Quadrant**
- Intestinal: acute appendicitis, regional enteritis, incarcerated hernia, cecal diverticulitis, intestinal obstruction, perforated ulcer, perforated cecum, Meckel’s diverticulitis
- Reproductive: ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, salpingitis, tubo-ovarian abscess, mittelschmerz, endometriosis, seminal vesiculitis
- Renal: renal and ureteral calculi, neoplasms, pyelonephritis
- Vascular: leaking aortic aneurysm
- Psoas abscess
- Trauma
- Cholecystitis

**Left Lower Quadrant**
- Intestinal: diverticulitis, intestinal obstruction, perforated ulcer, IBD, perforated descending colon, inguinal hernia, neoplasm, appendicitis
- Reproductive: ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, tubo-ovarian abscess, mittelschmerz, endometriosis, seminal vesiculitis
- Renal: renal or ureteral calculi, pyelonephritis, neoplasm
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Vascular: leaking aortic aneurysm  
Psoas abscess  
Trauma

3 ABORTION, RECURRENT
Congenital anatomic abnormalities  
Adhesions (uterine synechiae)  
Uterine fibroids  
Bicornuate uterus  
Endometriosis  
Endocrine abnormalities (luteal phase insufficiency, hypothyroidism, uncontrolled DM)  
Parental chromosome abnormalities  
Maternal infections (cervical *Mycoplasma, Ureaplasma, Chlamydia* infection)  
Diethylstilbestrol (DES) exposure, heavy metal exposure  
Thrombocytosis  
Allogenic immunity, autoimmunity, antiphospholipid syndrome, lupus anticoagulant and other thrombophilias

4 ACHES AND PAINS, DIFFUSE
Postviral arthralgias/myalgias  
Bilateral soft tissue rheumatism  
Overuse syndromes  
Fibrositis  
Hypothyroidism  
Metabolic bone disease  
Paraneoplastic syndrome  
Myopathy (polymyositis, dermomyositis)  
RA  
Sjögren’s syndrome  
Polymyalgia rheumatica  
Hypermobility  
Benign arthralgias/myalgias  
Chronic fatigue syndrome  
Hypophosphatemia  
Hypercalcemia  
Statins

5 ADNEXAL MASS
Ovary (neoplasm, endometriosis, functional cyst)  
Fallopian tube (ectopic pregnancy, neoplasm, tubo-ovarian abscess, hydrosalpinx, paratubal cyst)  
Uterus (fibroid, neoplasm)  
Retropertitoneum (neoplasm, abdominal wall hematoma or abscess)  
Urinary tract (pelvic kidney, distended bladder, urachal cyst)  
IBD  
GI tract neoplasm  
Diverticular disease  
Appendicitis  
Bowel loop w/feces

6 ADRENAL MASSES
Unilateral Adrenal Mass  
**Functional Lesions**  
Adrenal adenoma  
Adrenal carcinoma  
Pheochromocytoma  
Primary aldosteronism, adenomatous type  
**Nonfunctional Lesions**  
Incidentaloma of adrenal gland  
Ganglioneuroma  
Myelolipoma  
Hematoma  
Adenolipoma  
Metastasis

Bilateral Adrenal Mass  
**Functional Lesions**  
ACTH–dependent Cushing’s syndrome  
Congenital adrenal hyperplasia  
Pheochromocytoma  
Conn’s syndrome, hyperplastic variety  
Micronodular adrenal disease  
Idiopathic bilateral adrenal hypertrophy  
**Nonfunctional Lesions**  
Infection (tuberculosis, fungi)  
Infiltration (leukemia, lymphoma)  
Replacement (amyloidosis)  
Hemorrhage  
Bilateral mets

7 ADYNAMIC ILEUS
Abdominal trauma  
Infection (retroperitoneal, pelvic, intrathoracic)  
Laparotomy  
Metabolic disease (hypokalemia)  
Renal colic  
Skeletal injury (rib fracture, vertebral fracture)  
Medications (e.g., narcotics)

8 AEROPHAGIA
Anxiety disorders  
Rapid food ingestion  
Carbonated beverages  
Nursing infants (especially when nursing in horizontal position)  
Eating or drinking in supine position  
Gum chewing  
Poorly fitting dentures, orthodontic appliances  
Hiatal hernia, gastritis, nonulcer dyspepsia  
Cholelithiasis, cholecystitis  
Ingestion of legumes, onions, peppers
9 ALVEOLAR CONSOLIDATION

Infection
Neoplasm (bronchoalveolar carcinoma, lymphoma)
Aspiration
Trauma
Hemorrhage (Wegener’s granulomatosis, Goodpasture’s syndrome, bleeding diathesis)
ARDS
CHF
Renal failure
Eosinophilic pneumonia
Bronchiolitis obliterans
Pulmonary alveolar proteinosis

10 ALVEOLAR HEMORRHAGE

Hematologic disorders (coagulopathies, thrombocytopenia)
Goodpasture’s syndrome (anti–basement membrane Ab disease)
Wegener’s vasculitis
Immune complex–mediated vasculitis
Idiopathic pulmonary hemosiderosis
Drugs (penicillamine)
Lymphangiographic contrast medium
Mitral stenosis
Trauma

11 AMENORRHEA

Pregnancy, early menopause
Hypothalamic dysfunction: defective synthesis or release of luteinizing hormone–releasing hormone, anorexia nervosa, stress, exercise
Pituitary dysfunction: neoplasm, postpartum hemorrhage, surgery, radiotherapy
Ovarian dysfunction: gonadal dysgenesis, 17α-hydroxylase deficiency, premature ovarian failure, polycystic ovarian disease, gonadal stromal tumors
Uterovaginal abnormalities:
Congenital: imperforate hymen, imperforate cervix, imperforate or absent vagina, müllerian agenesis
Acquired: destruction of endometrium w/curettage (Asherman’s syndrome), closure of cervix or vagina caused by traumatic injury, hysterectomy
Other: androgen insensitivity (testicular feminization), metabolic diseases (liver, kidney), malnutrition, rapid weight loss, exogenous obesity, endocrine abnormalities (Cushing’s syndrome, Graves’ disease, hypothyroidism)

12 AMNESIA

Degenerative diseases (e.g., Alzheimer’s, Huntington’s disease)
CVA (especially when involving thalamus, basal forebrain, and hippocampus)
Head trauma
Postsurgical (e.g., mammillary body surgery, bilateral temporal lobectomy)
Infections (herpes simplex encephalitis, meningitis)
Wernicke-Korsakoff syndrome
Cerebral hypoxia
Hypoglycemia
CNS neoplasms
Creutzfeldt-Jakob disease
Medications (e.g., midazolam and other benzos)
Psychosis
Malingering

13 ANAL INCONTINENCE

Traumatic
Nerve injured in surgery
Obstetric trauma
Sphincter injury

Neurologic
Spinal cord lesions
Dementia
Autonomic neuropathy (e.g., DM)
Obstetrics: pudendal nerve stretched during surgery
Hirschsprung’s disease

Mass Effect
Carcinoma of anal canal
Carcinoma of rectum
Foreign body
Fecal impaction
Hemorrhoids

Medical
Procidentia
Inflammatory disease
Diarrhea
Laxative abuse

Pediatric
Congenital
Meningocele
Myelomeningocele
Spina bifida
After corrective surgery for imperforate anus
Sexual abuse
Encopresis
Chapter 2 The Differential Diagnosis: Zebras or Horses?

14 **ANISOCORIA**
- Mydriatic or miotic drugs
- Prosthetic eye
- Inflammation (keratitis, iridocyclitis)
- Infections (herpes zoster, syphilis, meningitis, encephalitis, tuberculosis, diphtheria, botulism)
- Subdural hemorrhage
- Cavernous sinus thrombosis
- Intracranial neoplasm
- Cerebral aneurysm
- Glaucoma
- CNS degenerative diseases
- Internal carotid ischemia
- Toxic polyneuritis (alcohol, lead)
- Adie’s syndrome
- Horner’s syndrome
- DM
- Trauma
- Congenital

15 **ANO VULATION**
- Anorexia and bulimia
- Strenuous exercise
- Weight loss/malnutrition
- Empty sella syndrome
- Pituitary disorders (infarction, infection, trauma, irradiation, surgery, microadenomas, macroadenomas)
- Idiopathic hypopituitarism
- Drug induced
- Thyroid dysfunction (hypothyroidism, hyperthyroidism)
- Systemic diseases (e.g., liver disease)
- Adrenal hyperfunction (Cushing’s syndrome, congenital adrenal hyperplasia)
- Polycystic ovarian syndrome
- Isolated gonadotropin deficiency

16 **ARTERIAL OCCLUSION**
- Thromboembolism (post MI, mitral stenosis, rheumatic valve disease, AF, atrial myxoma, marantic endocarditis, bacterial endocarditis, Libman-Sacks endocarditis; paradoxical embolism)
- Atheroembolism (microemboli composed of cholesterol, Ca, and platelets from proximal atherosclerotic plaques)
- Arterial thrombosis (endothelial injury, altered arterial blood flow, trauma, severe atherosclerosis, acute vasculitis)
- Vasospasm
- Trauma
- Hypercoagulable states
- Miscellaneous (irradiation, drugs, infections, necrosis)

17 **ARTHRITIS AND EYE LESIONS**
- SLE
- Sjögren’s syndrome
- Behçet’s syndrome
- Sarcoidosis
- Subacute bacterial endocarditis
- Lyme disease
- Wegener’s granulomatosis
- Giant cell arteritis
- Takayasu’s arteritis
- RA, juvenile RA
- Scleroderma
- IBD
- Whipple’s disease
- Ankylosing spondylitis
- Reactive arthritis
- Psoriatic arthritis

18 **ARTHRITIS AND HEART MURMUR**
- Subacute bacterial endocarditis
- Cardiac myxoma
- Ankylosing spondylitis
- Reactive arthritis
- Acute rheumatic fever
- RA
- SLE w/Libman-Sacks endocarditis
- Relapsing polychondritis

19 **ARTHRITIS AND MUSCLE WEAKNESS**
- RA
- Ankylosing spondylitis
- Polymyositis
- Dermatomyositis
- SLE, scleroderma, MCTD
- Sarcoidosis
- HIV-associated arthritis
- Whipple’s disease

20 **ARTHRITIS AND RASH**
- Chronic urticaria
- Vasculitic urticaria
- SLE
- Dermatomyositis
- Polymyositis
- Psoriatic arthritis
- Reactive arthritis
- Chronic sarcoidosis
- Serum sickness
- Sweet’s syndrome
- Leprosy
- Juvenile RA
- Rubella
- Erythema nodosum

21 **ARTHRITIS AND SUBCUTANEOUS NODULES**
- RA
- Gout
- Pseudogout (rare)
Sarcoidosis
Light chain amyloidosis (primary, MM)
Acute rheumatic fever
Hemochromatosis
Whipple’s disease
Multicentric reticulohistiocytosis

22 ARTHRITIS AND WEIGHT LOSS

Severe RA
RA w/vasculitis
Reactive arthritis
RA or psoriatic arthritis or ankylosing spondylitis w/amyloidosis
Cancer
Enteropathic arthritis (Crohn’s disease, UC)
HIV infection
Whipple’s disease
Blind loop syndrome
Scleroderma w/intestinal bacterial overgrowth

23 ARTHRITIS, FEVER, AND RASH

Rubella, parvovirus B19
Gonococemia, meningococemia
Secondary syphilis, Lyme borreliosis
Adult acute rheumatic fever, adult Still’s disease, adult Kawasaki disease
Vasculitic urticaria
Acute sarcoidosis
Familial Mediterranean fever
Hyperimmunoglobulinemia D and periodic fever syndrome

24 ARTHRITIS, MONARTICULAR AND OLIGOARTICULAR

Septic arthritis (Staphylococcus aureus, Neisseria gonorrhoeae, meningococci, streptococci, Streptococcus pneumoniae, enteric gram-negative bacilli)
Crystalline-induced arthritis (gout, pseudogout, Ca oxalate, hydroxyapatite, and other basic Ca/phosphate crystals)
Traumatic joint injury
Hemarthrosis
Monarticular or oligoarticular flare of an inflammatory polyarticular rheumatic disease (RA, psoriatic arthritis, Reiter’s syndrome, SLE)

25 ARTHRITIS, POLYARTICULAR

RA, juvenile (rheumatoid) polyarthritis
SLE, other connective tissue diseases, erythema nodosum, palindromic rheumatism, relapsing polychondritis
Psoriatic arthritis, ankylosing spondylitis
Sarcoidosis
Lyme arthritis, bacterial endocarditis, Neisseria gonorrhoeae infection, rheumatic fever, Reiter’s disease
Crystal deposition disease
Hypersensitivity to serum or drugs
Hepatitis B, HIV infection, rubella, mumps
Other: serum sickness, leukemias, lymphomas, enteropathic arthropathy, Whipple’s disease, Behçet’s syndrome, Henoch-Schönlein purpura, familial Mediterranean fever, hypertrophic pulmonary osteoarthropathy

26 ATAXIA

Vertebral-basilar artery ischemia
Diabetic neuropathy
Tabes dorsalis
Vitamin B12 deficiency
MS and other demyelinating diseases
Meningomyelopathy
Cerebellar neoplasms, hemorrhage, abscess, infarct
Nutritional (Wernicke’s encephalopathy)
Paraneoplastic syndromes
Parainfectious: GBS, acute ataxia of childhood and young adults
Toxins: phenytoin, alcohol, sedatives, organophosphates
Wilson’s disease (hepatolenticular degeneration)
Hypothyroidism
Myopathy
Cerebellar and spinocerebellar degeneration: ataxia-telangiectasia, Friedreich’s ataxia
Frontal lobe lesions: tumors, thrombosis of anterior cerebral artery, hydrocephalus
Labyrinthine destruction: neoplasm, injury, inflammation, compression
Hysteria
AIDS

27 AV NODAL BLOCK

Idiopathic fibrosis (Lenegre’s disease)
Sclerodegenerative processes (e.g., Lev’s disease w/calcification of the mitral and aortic annuli)
AV node radiofrequency ablation procedure
Medications (e.g., digoxin, β-blockers, CCBs, class III antiarrhythmics)
Acute inferior wall MI
Myocarditis
Infections (endocarditis, Lyme disease)
Infiltrative diseases (e.g., hemochromatosis, sarcoidosis, amyloidosis)
Trauma (including cardiac surgical procedures)
Collagen-vascular diseases
Aortic root diseases (e.g., spondylitis)
Electrolyte abnormalities (e.g., hyperkalemia)

28 BACK PAIN
Trauma: injury to bone, joint, or ligament
Mechanical: pregnancy, obesity, fatigue, scoliosis
Degenerative: osteoarthritis
Infections: osteomyelitis, subarachnoid or spinal abscess, tuberculosis, meningitis, basilar pneumonia
Metabolic: osteoporosis, osteomalacia
Vascular: leaking aortic aneurysm, subarachnoid or spinal hemorrhage/infarction
Neoplastic: myeloma, Hodgkin’s disease, carcinoma of pancreas; metastatic neoplasm from breast, prostate, lung
GI: penetrating ulcer, pancreatitis, cholelithiasis, IBD
Renal: hydronephrosis, calculus, neoplasm, renal infarction, pyelonephritis
Hematologic: sickle cell crisis, acute hemolysis
Gynecologic: neoplasm of uterus or ovary, dysmenorrhea, salpingitis, uterine prolapse
Inflammatory: ankylosing spondylitis, psoriatic arthritis, Reiter’s syndrome
Lumbosacral strain
Psychogenic: malingering, hysteria, anxiety
Endocrine: adrenal hemorrhage or infarction
Blood transfusion reaction

29 BONE PAIN
Trauma
Neoplasm (primary or metastatic)
Osteoporosis w/compression fracture
Paget’s disease of bone

Infection (osteomyelitis, septic arthritis)
Osteomalacia
Viral syndrome
Sickle cell disease
Anxiety

30 BRADYCARDIA, SINUS
Idiopathic
Degenerative processes (e.g., Lev’s disease, Lenegre’s disease)
Medications
β-Blockers
Some CCBs (diltiazem, verapamil)
Digoxin (when vagal tone is high)
Class I antiarrhythmic agents (e.g., procainamide)
Class III antiarrhythmic agents (amiodarone, sotalol)
Lithium carbonate
Acute myocardial ischemia and infarction
Right or left circumflex coronary artery occlusion or spasm
High vagal tone (e.g., athletes)

SSS

31 BREAST INFLAMMATORY LESION
Mastitis (Staphylococcus aureus, beta-hemolytic streptococcus)
Trauma
Foreign body (sutures, breast implants)
Granuloma (tuberculosis, fungal)
Fat necrosis post Bx
Necrosis or infarction (anticoagulant therapy, pregnancy)
Breast malignant neoplasm

32 BREAST MASS
Fibrocystic breasts
Benign tumors (fibroadenoma, papilloma)
Mastitis (acute bacterial mastitis, chronic mastitis)
Malignant neoplasm
Fat necrosis
Hematoma
Duct ectasia
Mammary adenosis

33 BREATH ODOR
Sweet, fruity: DKA, starvation ketosis
Fishy, stale: uremia (trimethylamines)
Ammonia-like: uremia (ammonia)
Musty fish, clover: fetor hepaticus (hepatic failure)
Foul, feculent: intestinal obstruction/diverticulum
Chapter 2  The Differential Diagnosis: Zebras or Horses?

Foul, putrid: nasal/sinus pathology (infection, foreign body, cancer), respiratory infections (empyema, lung abscess, bronchiectasis)

Achalasia

Halitosis: tonsillitis, gingivitis, respiratory infections, Vincent’s angina, gastroesophageal reflux

Cinnamon: pulmonary tuberculosis

**34 BREATHING, NOISY**

Infection: URI, peritonsillar abscess, retropharyngeal abscess, epiglottitis, laryngitis, tracheitis, bronchitis, bronchiolitis

Irritants and allergens: hyperactive airway, asthma (reactive airway disease), rhinitis, angioneurotic edema

Compression from outside of the airway: esophageal cysts or foreign body, neoplasms, lymphadenopathy

Congenital malformation and abnormality: vascular rings, laryngeal webs, laryngomalacia, tracheomalacia, hemangiomomas within the upper airway, stenoses within the upper airway, cystic fibrosis

Acquired abnormality (at every level of the airway): nasal polyps, hypertrophied adenoids or tonsils, foreign body, intraluminal tumors, bronchiectasis

Neurogenic disorder: vocal cord paralysis

**35 BULLOUS DISEASES**

Bullous pemphigoid

Pemphigus vulgaris

Pemphigus foliaceus

Paraneoplastic pemphigus

Cicatricial pemphigoid

Erythema multiforme

Dermatitis herpetiformis

Herpes gestationis

Impetigo

Erosive lichen planus

Linear IgA bullous dermatosis

Epidermolysis bullosa acquisita

**37 CARDIAC ARREST, NONTRAUMATIC**

Cardiac (CAD, cardiomyopathies, structural abnormalities, valve dysfunction, arrhythmias)

Respiratory (upper airway obstruction, hypoventilation, PE, asthma, COPD exacerbation, pulmonary edema)

Circulatory (tension pneumothorax, pericardial tamponade, pulmonary embolus, hemorrhage, sepsis)

Electrolyte abnormalities (hypokalemia or hyperkalemia, hypomagnesemia or hypermagnesemia, hypocalcemia)

Medications (tricyclic antidepressants, digoxin, theophylline, CCBs)

Drug abuse (cocaine, heroin, amphetamines)

Toxins (CO, cyanide)

Environmental (drowning/near-drowning, electrocution, lightning, hypothermia or hyperthermia, venomous snakes)

**38 CARDIAC ENLARGEMENT**

Cardiac Chamber Enlargement

Chronic volume overload

Mitral or aortic regurgitation

Left-to-right shunt (PDA, VSD, AV fistula)

Cardiomyopathy

Ischemic

Nonischemic

Decompensated pressure overload

AS

HTN

High-output states

Severe anemia

Thyrotoxicosis

Bradycardia

Severe sinus bradycardia

Complete heart block

Left Atrium

LV failure of any cause

Mitral valve disease

Myxoma

**Right Ventricle**

Chronic LV failure of any cause

Chronic volume overload

Tricuspid or pulmonic regurgitation

Left-to-right shunt (ASD)

Decompensated pressure overload

Pulmonic stenosis

PA HTN

Primary

Secondary (PE, COPD)

Pulmonary veno-occlusive disease

**36 CALCIFICATION ON CHEST X-RAY**

Lung neoplasm (primary or metastatic)

Silicosis

IPF

Tuberculosis

Histoplasmosis

Disseminated varicella infection

Mitral stenosis (end-stage)

Secondary hyperparathyroidism
Chapter 2  The Differential Diagnosis: Zebras or Horses?

**Right Atrium**
- RV failure of any cause
- Tricuspid valve disease
- Myxoma
- Ebstein’s anomaly

**Multichamber Enlargement**
- Hypertrophic cardiomyopathy
- Acromegaly
- Severe obesity

**Pericardial Disease**
- Pericardial effusion w/ or w/o tamponade
- Effusive constrictive disease
- Pericardial cyst, loculated effusion

**Pseudocardiomegaly**
- Epicardial fat
- Chest wall deformity (pectus excavatum, straight back syndrome)
- Low lung volumes
- AP chest x-ray
- Mediastinal tumor, cyst

**CARDIAC MURMURS**

**Systolic**
- MR
- TR
- VSD
- AS
- Idiopathic hypertrophic subaortic stenosis
- Pulmonic stenosis
- Innocent murmur of childhood
- Coarctation of aorta
- MVP

**Diastolic**
- Aortic regurgitation
- Atrial myxoma
- Mitral stenosis
- PA branch stenosis
- Tricuspid stenosis
- Graham Steell murmur (diastolic decrescendo murmur heard in severe pulmonary HTN)
- Pulmonic regurgitation
- Severe MR
- Austin Flint murmur (diastolic rumble heard in severe aortic regurgitation)
- Severe VSD and PDA

**Continuous**
- Patent ductus arteriosus
- Pulmonary AV fistula

**CAVITARY LESION ON CHEST X-RAY**

**Necrotizing Infections**
- Mycobacteria: *Mycobacterium tuberculosis*, *Mycobacterium kansasii*, *Mycobacterium avium-intracellulare*
- Bacteria-like: *Nocardia* species
- Fungi: *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces hominis*, *Aspergillus* species, *Mucor* species
- Parasitic: *Entamoeba histolytica*, *Echinococcus*, *Paragonimus westermani*

**Cavitary Infarction**
- Bland infarction (w/ or w/o superimposed infection)
- Lung contusion

**Septic Embolism**
- *Staphylococcus aureus*
- Anaerobes
- Others

**Vasculitis**
- Wegener’s granulomatosis
- Periarteritis

**Neoplasms**
- Bronchogenic carcinoma
- Metastatic carcinoma
- Lymphoma

**Miscellaneous Lesions**
- Cysts, blebs, bullae, or pneumatocele w/ or w/o fluid collections
- Sequestration
- Empyema w/air-fluid level
- Bronchiectasis

**CHEST PAIN (NONPLEURITIC)**

- Cardiac: myocardial ischemia/infarction, myocarditis
- Esophageal: spasm, esophagitis, ulceration, neoplasm, achalasia, diverticula, foreign body
- Referred pain from subdiaphragmatic GI structures:
  - Gastric and duodenal: hiatal hernia, neoplasm, PUD
  - Gallbladder and biliary: choledolithiasis, impacted stone, neoplasm
  - Pancreatic: pancreatitis, neoplasm
- Dissecting aortic aneurysm
- Pain originating from skin, breasts, and musculoskeletal structures: herpes zoster, mastitis, chest wall phlebitis, cervical spondylitis
- Mediastinal tumors: lymphoma, thymoma
Chapter 2  The Differential Diagnosis: Zebras or Horses?

Pulmonary: neoplasm, pneumonia, pulmonary embolism/infarction
Psychoneurosis
Chest pain associated w/MVP

CHEST PAIN (PLEURITIC)

Cardiac: pericarditis, postpericardiotomy/Dressler’s syndrome
Pulmonary: pneumothorax, hemothorax, embolism/infarction, pneumonia, empyema, neoplasm, bronchiectasis, pneumomediastinum, tuberculosis, carcinomatous effusion
GI: liver abscess, pancreatitis, esophageal rupture, Whipple’s disease w/associated pericarditis or pleuritis
Subdiaphragmatic abscess
Pain originating from skin and musculoskeletal tissues: costochondritis, chest wall trauma, fractured rib, interstitial fibrosis, myositis, strain of pectoralis muscle, herpes zoster, soft tissue and bone tumors
Collagen-vascular diseases w/pleuritis
Psychoneurosis

CLUBBING

Pulmonary neoplasm (lung, pleura)
Other neoplasm (GI, liver, Hodgkin’s, thymus, osteogenic sarcoma)
Pulmonary infectious process (empyema, abscess, bronchiectasis, tuberculosis, chronic pneumonitis)
Extrapulmonary infectious process (subacute bacterial endocarditis, intestinal tuberculosis, bacterial or amebic dysentery, arterial graft sepsis)
Pneumoconiosis
Cystic fibrosis
Sarcoidosis
Cyanotic CHD
Endocrine (Graves’ disease, hyperparathyroidism)
IBD
Celiac disease
Chronic liver disease, cirrhosis (particularly biliary and juvenile)
Pulmonary arteriovenous malformations
Idiopathic
Thyroid acropachy
Hereditary (pachydermoperiostosis)
Chronic trauma (e.g., in jackhammer operators, machine workers)

COLOR CHANGES, CUTANEOUS

Brown
Generalized: pituitary, adrenal, or liver disease; ACTH-producing tumor (e.g., oat cell lung carcinoma)
Localized: nevi, neurofibromatosis

White
Generalized: albinism, anemia
Localized: vitiligo, Raynaud’s syndrome

Red (Erythema)
Generalized: fever, polycythemia, urticaria, viral exanthems
Localized: inflammation, infection, Raynaud’s syndrome

Yellow
Generalized: liver disease, chronic renal disease, anemia
Generalized (except sclera): hypothyroidism, ↑ intake of vegetables containing carotene
Localized: resolving hematoma, infection, peripheral vascular insufficiency

Blue
Lips, mouth, nail beds: CV and pulmonary diseases, Raynaud’s syndrome

COMA

Vascular: hemorrhage, thrombosis, embolism
CNS infections: meningitis, encephalitis, cerebral abscess
Cerebral neoplasms w/herniation
Head injury: subdural hematoma, cerebral concussion, cerebral contusion
Drugs: narcotics, sedatives, hypnotics
Ingestion or inhalation of toxins: CO, alcohol, lead
Metabolic disturbances:
Hypoxia
Acid-base disorders
Hypoglycemia, hyperglycemia
Hepatic failure
Electrolyte disorders
Uremia
Hypothyroidism
Hypothermia, hyperthermia
Hypotension, malignant HTN
Postictal
Meningeal Disorders
Bacterial meningitis
Encephalitis

Exogenous Toxins
Sedatives and barbiturates
Anesthetics and γ-hydroxybutyrate
Alcohols
Stimulants
Phencyclidine
Cocaine and amphetamine
Psychotropic drugs
Tricyclic antidepressants
Phenothiazines
Lithium
Anticonvulsants
Opioids
Clonidine
PCNs
Salicylates
Anticholinergics
CO, cyanide, and methemoglobinemia

Endogenous Toxins, Deficiencies, and Derangements
Hypoxia and ischemia
Hypoglycemia
Hypercalcemia
Osmolar
Hyperglycemia
Hyponatremia
Hypernatremia
Hypermagnesemia
Organ system failure
Hepatic encephalopathy
Uremic encephalopathy
Pulmonary insufficiency (carbon dioxide narcosis)

Seizures
Prolonged postictal state
Spike-wave stupor
Status epilepticus

Hypothermia or Hyperthermia
Brainstem ischemia
Basilar artery stroke
Conversion or malingering

Constipation
Intestinal obstruction:
Fecal impaction
Diverticular disease
GI neoplasm
Strangulated femoral hernia
Gallstone ileus
Tuberculous stricture
Adhesions
Ameboma
Volvulus
Intussusception
IBD
Hematoma of bowel wall, secondary to trauma or anticoagulants

Poor dietary habits: insufficient bulk in diet, inadequate fluid intake
Change from daily routine: travel, hospital admission, physical inactivity
Acute abdominal conditions: renal colic, salpingitis, biliary colic, appendicitis, ischemia
Hypercalcemia or hypokalemia, uremia
IBS, pregnancy, anorexia nervosa, depression

Painful anal conditions:
hemorrhoids, fissure, stricture

Intestinal periasticls: old age, spinal cord injuries, myxedema, diabetes, MS, parkinsonism and other neurologic diseases

Drugs: codeine, morphine, antacids w/aluminum, verapamil, anticonvulsants, anticholinergics, disopyramide, cholestyramine, alosetron, iron supplements
Hirschsprung’s disease, meconium ileus, congenital atresia in infants

Cough
Infectious process (viral, bacterial)
Post infection
“Smoker’s cough”
Rhinitis (allergic, vasomotor, postinfectious)

Asthma
Exposure to irritants (noxious fumes, smoke, cold air)

Drug induced (especially ACEIs, β-blockers)
GERD
ILD
Lung neoplasms
Lymphomas, mediastinal neoplasms
Bronchiectasis

* General anesthetic, similar to γ-aminobutyric acid; recreational drug and body building aid. Rapid onset, rapid recovery often with myoclonic jerking and confusion. Deep coma (2-3 hr; Glasgow Coma Scale = 3) with maintenance of vital signs.
† Coma associated with cholinergic signs: lacrimation, salivation, bronchorrhea, and hyperthermia.
§ An antihypertensive agent active through the opiate receptor system; frequent overdose when used to treat narcotic withdrawal.
‡ Coma after seizures or status (i.e., a prolonged postictal state).
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Cardiac (CHF, pulmonary edema, mitral stenosis, pericardial inflammation)
Recurrent aspiration
Inflammation of larynx, pleura, diaphragm, mediastinum
Cystic fibrosis
Anxiety
Other: PE, foreign body inhalation, aortic aneurysm, Zenker’s diverticulum, osteophytes, substernal thyroid, thyroiditis

**CRYSTAL DEPOSITION ARTHRITIDES**

See Table 2-1.

**CYANOSIS**

CHD w/right-to-left shunt PE

---

<table>
<thead>
<tr>
<th>Crystal-Induced Arthritis</th>
<th>Characteristics of Crystals (from Joint Aspiration)</th>
<th>Commonly Involved Joints</th>
<th>Comments and Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gouty arthritis</td>
<td>Monosodium urate crystals</td>
<td>First metatarsophalangeal, ankles, midfoot</td>
<td>See Chapter 3</td>
</tr>
<tr>
<td>Ca pyrophosphate deposition disease (pseudogout)</td>
<td>Ca pyrophosphate dihydrate crystals Rhomboid or polymorphic, weakly positive, birefringent crystals</td>
<td>Knees, wrists</td>
<td>X-rays of involved joint may reveal linear calcifications (chondrocalcinosis) on articular cartilage Possible associated conditions must be ruled out: Hyperparathyroidism Hypothyroidism Hemochromatosis Hypomagnesemia Therapy: NSAIDs, joint immobilization, intra-articular steroids</td>
</tr>
<tr>
<td>Hydroxyapatite arthropathy</td>
<td>Ca hydroxyapatite crystals Crystals form non-birefringent clumps w/ synovial fluid when placed on slide Dx often requires microscopy because of the small size of the crystals</td>
<td>Knees, hips, shoulders</td>
<td>Usually affects younger pts than the other crystal-induced arthritides do Therapy: NSAIDs, joint immobilization, intra-articular steroids</td>
</tr>
<tr>
<td>Ca oxalate-induced arthritis</td>
<td>Ca oxalate crystals Bipyramidal, positive birefringent crystals</td>
<td>DIP, PIP joints of hands</td>
<td>Often seen in dialysis pts taking large doses of ascorbic acid (metabolized to oxalate) Therapy: NSAIDs, joint immobilization, intra-articular steroids</td>
</tr>
</tbody>
</table>

DIP, distal interphalangeal; PIP, proximal interphalangeal.
Chapter 2  The Differential Diagnosis: Zebras or Horses?

Hypoxia
Pulmonary edema
Pulmonary disease (oxygen diffusion and alveolar ventilation abnormalities)
Hemoglobinopathies
↓ CO
Vasospasm
Arterial obstruction
Pulmonary arteriovenous fistulas
Elevated hemidiaphragm
Neoplasm (bronchogenic carcinoma, mediastinal neoplasm, intrahepatic lesion)
Substernal thyroid
Infectious process (pneumonia, empyema, tuberculosis, subphrenic abscess, hepatic abscess)
Atelectasis
Idiopathic
Eventration of diaphragm
Phrenic nerve dysfunction (myelitis, myotonia, herpes zoster)
Trauma to phrenic nerve or diaphragm (e.g., surgery)
Thoracic aortic aneurysm
Intra-abdominal mass
Pulmonary infarction
Pleurisy
Radiation therapy
Rib fracture
Superior vena cava syndrome

51 DEMYELINATING DISEASES

Multiple Sclerosis
Relapsing and chronic progressive forms
Acute MS
Neuromyelitis optica (Devic’s disease)
GBS

Diffuse Cerebral Sclerosis
Schilder’s encephalitis periaxialis diffusa
Balo’s concentric sclerosis

Acute Disseminated Encephalomyelitis
After measles, chickenpox, rubella, influenza, mumps
After rabies or smallpox vaccination

Necrotizing Hemorrhagic Encephalitis
Hemorrhagic leukoencephalitis

Leukodystrophies
Krabbe’s globoid leukodystrophy
Metachromatic leukodystrophy
Adrenoleukodystrophy
Adrenomyeloneuropathy

Pelizaeus-Merzbacher leukodystrophy
Canavan’s disease
Alexander’s disease

52 DIARRHEA, TUBE-FED PATIENT

Common Causes Unrelated to Tube Feeding
Elixir medications containing sorbitol
Magnesium-containing antacids
Abx-induced sterile gut
Pseudomembranous colitis

Possible Causes Related to Tube Feeding
Inadequate fiber to form stool bulk
High fat content of formula (in the presence of fat malabsorption syndrome)
Bacterial contamination of enteral products and delivery systems (causal association w/diarrhea not documented)
Rapid advancement in rate (after the GI tract is unused for prolonged periods)

Unlikely Causes Related to Tube Feeding
Formula hyperosmolality (proven not to be the cause of diarrhea)
Lactose (absent from nearly all enteral feeding formulas)

53 DIPLOPIA, BINOCULAR

Cranial nerve palsy (third, fourth, sixth)
Thyroid eye disease
Myasthenia gravis
Decompensated strabismus
Orbital trauma w/blow-out fracture
Orbital pseudotumor
Cavernous sinus thrombosis

54 DRY EYE

Contacts
Medications (antihistamines, clonidine, β-blockers, ibuprofen, scopolamine)
Keratoconjunctivitis sicca
Trauma
Environmental causes (air conditioning in patient w/contacts)

55 DYSPHAGIA

Esophageal obstruction: neoplasm, foreign body, achalasia, stricture, spasm, esophageal web, diverticulum, Schatzki’s ring
Peptic esophagitis w/stricture, Barrett’s stricture
External esophageal compression: neoplasms (thyroid neoplasm,
The Differential Diagnosis: Zebras or Horses?

lymphoma, mediastinal tumors), thyroid enlargement, aortic aneurysm, vertebral spurs, aberrant right subclavian artery (dysphagia lusoria)
Hiatal hernia, GERD
Oropharyngeal lesions: pharyngitis, glossitis, stomatitis, neoplasms
Hysteria: globus hystericus
Neurologic or neuromuscular disturbances: bulbar paralysis, myasthenia gravis, amyotrophic lateral sclerosis, MS, parkinsonism, CVA, diabetic neuropathy
Toxins: poisoning, botulism, tetanus, postdiphtheritic dysphagia
Systemic diseases: scleroderma, amyloidosis, dermatomyositis
Candida and herpes esophagitis
Presbyesophagus

56 DYSPNEA
Upper airway obstruction: trauma, neoplasm, epiglottitis, laryngeal edema, tongue retraction, laryngospasm, abductor paralysis of vocal cords, aspiration of foreign body
Lower airway obstruction: neoplasm, COPD, asthma, aspiration of foreign body
Pulmonary infection: pneumonia, abscess, empyema, tuberculosis, bronchiectasis
Pulmonary HTN
Pulmonary embolism/infarction
Parenchymal lung disease
Pulmonary vascular congestion
Cardiac disease: atherosclerotic heart disease, valvular lesions, cardiac dysrhythmias, cardiomyopathy, pericardial effusion, cardiac shunts
Space-occupying lesions: neoplasm, large hiatal hernia, pleural effusions
Disease of chest wall: severe kyphoscoliosis, fractured ribs, sternal compression, morbid obesity
Neurologic dysfunction: GBS, botulism, polio, spinal cord injury
Interstitial pulmonary disease: sarcoidosis, collagen-vascular diseases, desquamative interstitial pneumonitis, Hamman-Rich pneumonitis, others
Pneumoconioses: silicosis, berylliosis, others
Mesothelioma
Pneumothorax, hemothorax, pleural effusion
Inhalation of toxins
Cholinergic drug intoxication
Carcinoid syndrome
Hematologic: anemia, polycythemia, hemoglobinopathies
Thyrotoxicosis, myxedema
Diaphragmatic compression caused by abdominal distention, subphrenic abscess, ascites
Lung resection
Metabolic abnormalities: uremia, hepatic coma, DKA
Sepsis
Atelectasis
Psychoneurosis
Diaphragmatic paralysis
Pregnancy

57 DYSURIA
UTI
Estrogen deficiency (in postmenopausal woman)
Vaginitis
Genital infection (e.g., herpes, condyloma)
Interstitial cystitis
Chemical irritation (e.g., deodorant aerosols, douches)
Meatal stenosis or stricture
Reiter’s syndrome
Bladder neoplasm
GI origin (diverticulitis, Crohn’s disease)
Impaired bladder or sphincter action
Urethral carbuncle
Chronic fibrosis post trauma
Radiation therapy
Prostatitis
Urethritis (gonococcal, chlamydial)
Behçet’s syndrome
Stevens-Johnson syndrome

58 DYSTONIA
Parkinson’s disease
Progressive supranuclear palsy
Wilson’s disease
Huntington’s disease
Drug effects

59 EARACHE
Otitis media
Serous otitis media
Eustachitis
Otitis externa
Otic barotrauma
Mastoiditis
Foreign body
Impacted cerumen
Referred otalgia, as w/ temporomandibular joint dysfunction, dental problems and tumors, thyroiditis
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ST-T CHANGES

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Normal</td>
</tr>
<tr>
<td>B</td>
<td>Early repolarization</td>
</tr>
<tr>
<td>C</td>
<td>Epicardial injury</td>
</tr>
<tr>
<td>D</td>
<td>Subendocardial injury</td>
</tr>
<tr>
<td>E</td>
<td>Digitalis</td>
</tr>
<tr>
<td>F</td>
<td>Hypokalemia quinidine, cerebral hemorrhage</td>
</tr>
<tr>
<td>G</td>
<td>Strain</td>
</tr>
</tbody>
</table>

**FIGURE 2-1.** ST-T wave changes in normal and abnormal conditions.

---

**60 ECG: ST-T WAVE CHANGES**

See Figure 2-1.

---

**61 ECG: T WAVE CHANGES**

See Figure 2-2.

---

**62 EDEMA, GENERALIZED**

CHF  Cirrhosis  Nephrotic syndrome  Pregnancy  Idiopathic  Acute nephritic syndrome  Myxedema  Medications (NSAIDs, estrogens, vasodilators), CCBs, glitazones

**63 EDEMA, LEG, UNILATERAL**

**With Pain**

DVT  Postphlebitic syndrome  Popliteal cyst rupture  Gastrocnemius rupture  Cellulitis  Psoas or other abscess

**Without Pain**

DVT  Postphlebitic syndrome  Other venous insufficiency (after saphenous vein harvest, varicosities)

---

**64 EDEMA OF LOWER EXTREMITIES**

CHF (right sided)  Hepatic cirrhosis  Nephrosis  Myxedema  Lymphedema  Pregnancy  Abdominal mass: neoplasm, cyst  Venous compression from abdominal aneurysm  Varicose veins  Bilateral cellulitis  Bilateral thrombophlebitis  Vena cava thrombosis, venous thrombosis  Retroperitoneal fibrosis

---

**65 ELEVATED HEMIDIAPHRAGM**

Neoplasm (bronchogenic carcinoma, mediastinal neoplasm, intrahepatic lesion)  Infectious process (pneumonia, empyema, tuberculosis, subphrenic abscess, hepatic abscess)  Atelectasis  Idiopathic  Eventration
Phrenic nerve dysfunction (myelitis, myotonia, herpes zoster, malignant neoplasm)
Trauma to phrenic nerve or diaphragm (e.g., surgery)
Aortic aneurysm
Intra-abdominal mass
Pulmonary infarction
Pleurisy
Radiation therapy
Rib fracture

66 EMBOLI, ARTERIAL
MI w/mural thrombi
AF
Cardiomyopathies
Prosthetic heart valves
CHF
Endocarditis
Left ventricular aneurysm
Left ventricular apical akinesis
Left atrial myxoma
SSS
Paradoxical embolus from venous thrombosis
Aneurysms of large blood vessels
Atheromatous ulcers of large blood vessels

67 ENCEPHALOPATHY, METABOLIC
Substrate deficiency: hypoxia/ischemia, CO poisoning, hypoglycemia
Cofactor deficiency: thiamine, vitamin B₁₂, pyridoxine (isoniazid administration)
Electrolyte disorders: hyponatremia, hypercalcemia, carbon dioxide narcosis, dialysis, hypermagnesemia, disequilibrium syndrome
Endocrinopathies: DKA, hyperosmolar coma, hypothyroidism, hyperadrenocorticism, hyperparathyroidism
Endogenous toxins: liver disease, uremia, porphyria
Exogenous toxins: drug OD (sedative-hypnotics, ethanol, narcotics, salicylates, tricyclic antidepressants), drug withdrawal, toxicity of therapeutic medications, industrial toxins (e.g., organophosphates, heavy metals), sepsis
Heat stroke
Epilepsy (postictal)
ICU encephalopathy (multifactorial)

68 EPILEPSY
Psychogenic spells
TIA
Hypoglycemia
Syncope
Narcolepsy
Migraine
Paroxysmal vertigo
Arrhythmias
Drug reaction

69 EPISTAXIS
Trauma
Medications (nasal sprays, NSAIDs, anticoagulants, antiplatelets)
Nasal polyps
Cocaine use
Coagulopathy (hemophilia, liver disease, disseminated intravascular coagulation, thrombocytopenia)
Systemic disorders (HTN, uremia)
Infections
Anatomic malformations
Rhinitis
Nasal polyps
Local neoplasms (benign and malignant)
Desiccation
Foreign body

70 ESOPHAGEAL PERFORATION
Trauma
Caustic burns
Iatrogenic
Foreign bodies
Spontaneous rupture (Boerhaave’s syndrome)
Postoperative breakdown of anastomosis

71 EYE PAIN
Foreign body
Herpes zoster
Trauma
Conjunctivitis
Iritis
Iridocyclitis
Uveitis
Blepharitis
Ingrown lashes
Orbital or periorbital cellulitis/abscess
Sinusitis
Headache
Glaucoma
Inflammation of lacrimal gland
Tic douloureux
Cerebral aneurysm
Cerebral neoplasm
Entropion
Retrobulbar neuritis
Ultraviolet light
Dry eyes
Irritation or inflammation from eye drops, dust, cosmetics, and the like

**72 FACIAL PAIN**
Infection, abscess
Postherpetic neuralgia
Trauma, post-traumatic neuralgia
Tic douloureux
Cluster headache, “lower-half headache”
Geniculate neuralgia
Anxiety, somatization syndrome
Glossopharyngeal neuralgia
Carotidynia
Giant cell arteritis

**73 FACIAL PARALYSIS**
**Infectious**
Bacterial: otitis media, mastoiditis, meningitis, Lyme disease
Viral: herpes zoster, mononucleosis, varicella, rubella, mumps, Bell’s palsy (likely HSV-1)
Mycobacterial: tuberculosis, meningitis, leprosy

**Traumatic**
Temporal bone fracture, facial laceration
Surgery

**Neoplastic**
Malignant: squamous cell carcinoma, basal cell and adenocystic tumors, leukemia, parotid neoplasms, metastatic tumors
Benign: facial nerve neuroma, vestibular schwannoma, congenital cholesteatoma

**Immunologic**
GBS, PAN
Reaction to tetanus antiserum

**Metabolic**
Pregnancy
Hypothyroidism
DM

**Other**
Sarcoidosis

**74 FATIGUE**
Depression
Anxiety, emotional stress
Inadequate sleep
Prolonged physical activity
Pregnancy and postpartum period
Anemia
Hypothyroidism

Medications (β-blockers, anxiolytics, antidepressants, sedating antihistamines, clonidine, methylpaprazil)
Viral or bacterial infections
Sleep apnea syndrome
Dieting
Renal failure, CHF, COPD, liver disease

**75 FATTY LIVER**
Obesity
Alcohol abuse
DM
Acute fatty liver of pregnancy
Medications (tetracycline, valproic acid, glucocorticoids, amiodarone, estrogen, methotrexate)
Reye’s syndrome
Wilson’s disease
Nonalcoholic steatohepatitis

**76 FEVER AND JAUNDICE**
Cholecystitis
Hepatic abscess (pyogenic, amebic)
Ascending cholangitis
Pancreatitis
Malaria
Neoplasm (hepatic, pancreatic, biliary tract, metastatic)
Mononucleosis
Viral hepatitis
Sepsis
Babesiosis
HIV infection (*Cryptosporidium*)
Biliary ascariasis
Toxic shock syndrome
Hemolytic anemia
*Yersinia* infection, leptospirosis, yellow fever, dengue fever, relapsing fever

**77 FEVER AND RASH**
Drug hypersensitivity: PCN, sulfonamides, thiazides, anticonvulsants, allopurinol
Viral infection: measles, rubella, varicella, erythema infectiosum, roseola, enterovirus infection, viral hepatitis, infectious mononucleosis, acute HIV infection
Other infections: meningococcemia, staphylococcemia, scarlet fever, typhoid fever, *Pseudomonas* bacteremia, RMSF, Lyme disease, secondary syphilis, bacterial endocarditis, babesiosis, brucellosis, listeriosis
Serum sickness
Erythema multiforme
Erythema marginatum
Erythema nodosum
Chapter 2  The Differential Diagnosis: Zebras or Horses?

SLE  Dermatomyositis  Allergic vasculitis  Pityriasis rosea  Herpes zoster  Sweet’s syndrome

78 FLANK PAIN
Urolithiasis  Radicular/muscular  Pyelonephritis  Herpes zoster  Renal abscess  Renal vein thrombosis  Renal infarction  AAA  Retroperitoneal hematoma

79 FLUSHING
Physiologic flushing: menopause, ingestion of monosodium glutamate (Chinese restaurant syndrome), ingestion of hot drinks  Drugs: alcohol (w/ or w/o disulfiram, metronidazole, or chlorpropamide), nicotinic acid, diltiazem, nifedipine, levodopa, bromocriptine, vancomycin, amyl nitrate  Neoplastic disorders: carcinoïd syndrome, vipsia syndrome, medullary carcinoma of thyroid, systemic mastocytosis, basophilic CML, renal cell carcinoma  Anxiety disorders  Metabolic abnormalities

80 GALACTORRHEA
Prolonged suckling  Drugs (isoniazid, phenothiazines, reserpine derivatives, amphetamines, spironolactone, tricyclic antidepressants)  Major stressors (surgery, trauma)  Hypothyroidism  Pituitary tumors

81 GASTRIC EMPTYING, DELAYED
Mechanical Obstruction  Duodenal or pyloric channel ulcer  Pyloric stenosis  Tumor of the distal stomach
Functional Obstruction (Gastroparesis)  Drugs: anticholinergics, α-adrenergics, opiates  Electrolyte imbalance: hypokalemia, hypocalcemia, hypomagnesemia  Metabolic disorders: DM, hypoparathyroidism, hypothyroidism, pregnancy  Vagotomy  Viral infections  Neuromuscular disorders (myotonic dystrophy, autonomic neuropathy, scleroderma, polymyositis)  Gastric pacemaker (i.e., tachygastria)  Brainstem tumors  GERD  Psychiatric disorders: anorexia nervosa, psychogenic vomiting  Idiopathic

82 GASTRIC EMPTYING, RAPID
Pancreatic insufficiency  Dumping syndrome  Peptic ulcer  Celiac disease  Promotility agents  Zollinger-Ellison disease

83 GENITAL DISCHARGE

84 GENITAL SORES
Herpes genitalis  Syphilis  Chancroid  Lymphogranuloma venereum  Granuloma inguinale  Condyloma acuminatum  Neoplastic lesion  Trauma

85 GOITER
Thyroiditis  Toxic multinodular goiter  Graves’ disease  Medications (propylthiouracil, methimazole, sulfonamides, sulfonylureas, ethionamide, amiodarone, lithium, others)  Iodine deficiency  Sarcoidosis, amyloidosis  Defective thyroid hormone synthesis
Chapter 2  The Differential Diagnosis: Zebras or Horses?

Resistance to thyroid hormone
Neoplasm

86 GRANULOMATOUS LUNG DISEASES
See Table 2-2 on page 116.

87 GYNECOMASTIA
Physiologic (puberty, newborns, aging)
Drugs (estrogen and estrogen precursors, digitals, testosterone and exogenous androgens, clomiphene, cimetidine, spironolactone, ketoconazole, amiodarone, ACEIs, isoniazid, phenytoin, methyldopa, metoclopramide, phenothiazine)
↑ Prolactin level (prolactinoma)
Liver disease
Adrenal disease
Thyrotoxicosis
↑ Estrogen production (human chorionic gonadotropin–producing tumor, testicular tumor, bronchogenic carcinoma)
Secondary hypogonadism
Primary gonadal failure (trauma, castration, viral orchitis, granulomatous disease)
Defects in androgen synthesis
Testosterone deficiency
Klinefelter’s syndrome

88 HALITOSIS
Tobacco use
Alcohol use
Dry mouth (mouth breathing, inadequate fluid intake)
Foods (onion, garlic, meats, nuts)
Disease of mouth or nose (infections, cancer, inflammation)
Medications (antihistamines, antidepressants)
Systemic disorders (diabetes, uremia, cirrhosis)
GI disorders (esophageal diverticula, hiatal hernia, GERD, achalasia)
Sinusitis
Tonsillitis
Pulmonary disorders (bronchiectasis, pneumonia, neoplasms, tuberculosis)

89 HEADACHE
Vascular: migraine, cluster headaches, temporal arteritis, HTN, cavernous sinus thrombosis
Musculoskeletal: neck and shoulder muscle contraction, strain of extraocular or intraocular muscles, cervical spondylosis, temporomandibular arthritis
Infections: meningitis, encephalitis, brain abscess, sepsis, sinusitis, osteomyelitis, parotitis, mastoiditis
Cerebral neoplasm
Subdural hematoma
Cerebral hemorrhage/infarct
Giant cell arteritis
Pseudotumor cerebri
NPH
Post lumbar puncture
Cerebral aneurysm, arteriovenous malformations
Post trauma
Dental problems: abscess, periodontitis, poorly fitting dentures
Trigeminal neuralgia, glossopharyngeal neuralgia
Otitis and other ear diseases
Glucoma and other eye diseases
Metabolic: uremia, CO inhalation, hypoxia
Pheochromocytoma, hypoglycemia, hypothyroidism
Effort induced: benign exertional headache, cough, headache, coital cephalalgia
Drugs: alcohol, nitrates, histamine antagonists
Paget’s disease of the skull
Emotional, psychiatric

90 HEARING LOSS, ACUTE
Infectious: mumps, measles, influenza, herpes simplex, herpes zoster, CMV, mononucleosis, syphilis
Vascular: macroglobulinemia, sickle cell disease, Berger’s disease, leukemia, polycythemia, fat emboli, hypercoagulable states
Metabolic: diabetes, pregnancy, hyperlipoproteinemia
Conductive: cerumen impaction, foreign bodies, otitis media, otitis externa, barotrauma, trauma
Medications: AGs, loop diuretics, antineoplastics, salicylates, vancomycin
Neoplasm: acoustic neuroma, metastatic neoplasm
Meniere’s disease

91 HEARTBURN AND INDIGESTION
Reflux esophagitis
Gastritis
Nonulcer dyspepsia
Functional GI disorder (anxiety disorder, social/environmental stresses)
<table>
<thead>
<tr>
<th>Feature</th>
<th><strong>Wegener’s Granulomatosis</strong></th>
<th><strong>Lymphomatoid Granulomatosis</strong></th>
<th><strong>Churg-Strauss Syndrome</strong></th>
<th><strong>Necrotizing Sarcoid Granulomatosis</strong></th>
<th><strong>Bronchocentric Granulomatosis</strong></th>
<th><strong>Sarcoidosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>M/F</td>
<td>Equal</td>
<td>Affects men slightly more frequently</td>
<td>Same</td>
<td>Same</td>
<td>F &gt; M</td>
</tr>
<tr>
<td><strong>Decade of incidence</strong></td>
<td>50s</td>
<td>50s</td>
<td>30s to 50s</td>
<td>50s</td>
<td>30s</td>
<td>30s and 40s</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Sinusitis Rhinorrhea Epistaxis</td>
<td>+</td>
<td>Cough Dyspnea Hemoptysis Arthralgia</td>
<td>Bronchitis Asthma Pneumonia</td>
<td>Fever Cough Pleurisy Malaise</td>
<td>Asthma Bronchiectasis Bronchial obstruction</td>
</tr>
<tr>
<td><strong>Ulcerated nose and nasal septum</strong></td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Eosinophilia</td>
<td>−</td>
</tr>
<tr>
<td><strong>Chest radiograph opacities</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Particularly in upper lobes</td>
<td>+</td>
</tr>
<tr>
<td><strong>Cavitation</strong></td>
<td>++</td>
<td>+</td>
<td>Infiltration +</td>
<td>Pulmonary fibrosis</td>
<td>Infiltration</td>
<td></td>
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<tr>
<td><strong>Hilar adenopathy</strong></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td><strong>Kidneys</strong></td>
<td>GN in 85%</td>
<td>−</td>
<td>Renal vasculitis</td>
<td>−</td>
<td>−</td>
<td>Nephrocalcinosis</td>
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<tr>
<td><strong>Ocular</strong></td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td><strong>Allergy</strong></td>
<td>±</td>
<td>±</td>
<td>−</td>
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<tr>
<td><strong>Skin lesions</strong></td>
<td>+</td>
<td>−</td>
<td>+</td>
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<tr>
<td><strong>CNS</strong></td>
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<td>−</td>
<td>Rare</td>
<td>Rare</td>
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<tr>
<td><strong>Cardiac</strong></td>
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<td>−</td>
<td>−</td>
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<tr>
<td><strong>Characteristics</strong></td>
<td>↑ ESR</td>
<td>−</td>
<td>Eosinophilia</td>
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<td>Hypersensitivity to Aspergillus Eosinophilia</td>
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<td><strong>Granulomas</strong></td>
<td>±</td>
<td>±</td>
<td>Very rare</td>
<td>Infrequent</td>
<td>Always</td>
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<tr>
<td><strong>Vasculitis</strong></td>
<td>++</td>
<td>++</td>
<td>Always</td>
<td>Always</td>
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<td><strong>Necrosis</strong></td>
<td>Prominent and resembling infarcts</td>
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<td><strong>Prognosis</strong></td>
<td>Poor</td>
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<td>Good</td>
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</table>

+, present; ++, prominent; −, absent; ±, inconspicuous; SACE, serum angiotensin-converting enzyme; SURT, sarcoidosis of upper respiratory tract.
Chapter 2  The Differential Diagnosis: Zebras or Horses?

Excessive intestinal gas (ingestion of flatulogenic foods, GI stasis, constipation)
Gas entrapment (hepatitis or splenic flexure syndrome)
Neoplasm (adenocarcinoma of stomach or esophagus, lymphoma)
Gallbladder disease

**HEMARTHROSIS**

Trauma
Anticoagulant therapy
Thrombocytopenia, thrombocytosis
Coagulation disorders (e.g., vWD, hemophilias)
Charcot’s joint
Idiopathic
Other: pigmented villonodular synovitis, hemangioma, synovioma, arteriovenous fistula, ruptured aneurysm

**HEMATURIA**

Use the mnemonic TICS:

T  
*Trauma*: blow to kidney, insertion of Foley catheter or foreign body in urethra, prolonged and severe exercise, very rapid emptying of overdistended bladder

*Tumor*: hypernephroma, Wilms’ tumor, papillary carcinoma of the bladder, prostatic and urethral neoplasms

*Toxins*: turpentine, phenols, sulfonamides and other Abx, cyclophosphamide, NSAIDs

I  
*Infections*: GN, tuberculosis, cystitis, prostatitis, urethritis, *Schistosoma haematobium* infection, yellow fever, blackwater fever

*Inflammatory processes*: Goodpasture’s syndrome, periarteritis, post irradiation

C  
*Calculi*: renal, ureteral, bladder, urethra

*Cysts*: simple cysts, polycystic disease

*Congenital anomalies*: hemangiomas, aneurysms, AV malformation

S  
*Surgery*: invasive procedures, prostatic resection, cystoscopy

*Sickle cell disease and other hematologic disturbances*: hemophilia, thrombocytopenia, anticoagulants

*Somewhere else*: bleeding genitals, factitious (e.g., in drug addicts)

**HEMIPARESIS/HEMIPLEGIA**

CVA
TIA
Cerebral neoplasm
MS or other demyelinating disorder
CNS infection
Migraine
Hypoglycemia
Subdural hematoma
Vasculitis
Todd’s paralysis
Epidural hematoma
Metabolic (hyperosmolar state, electrolyte imbalance)
Psychiatric disorders
Congenital disorders
Leukodystrophies

**HEMOLYSIS AND HEMOGLOBINURIA**

Erythrocyte trauma (prosthetic cardiac valves, marching and severe trauma, extensive burns)
Infections (malaria, *Bartonella, Clostridium welchii*)
Brown recluse spider bite
Incompatible blood transfusions
AIHAs
Hemolytic-uremic syndrome
TTP
PNH
Drugs (PCNs, quinidine, methyldopa, sulfonamides, nitrofurantoin)
Erythrocyte enzyme deficiencies (e.g., exposure to fava beans in pts w/glucose-6-phosphate dehydrogenase deficiency)

**HEMOPTYSIS**

**Cardiovascular**

Pulmonary embolism/infarction
Left ventricular failure
Mitral stenosis
Arteriovenous fistula
Severe HTN
Erosion of aortic aneurysm

**Pulmonary**

Neoplasm (primary or metastatic)
Infection:

Pneumonia: *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Legionella pneumophila*

Bronchiectasis
Abscess
Tuberculosis
Bronchitis
Fungal infections (aspergillosis, coccidioidomycosis)
Parasitic infections (amebiasis, ascariasis, paragonimiasis)
Vasculitis: Wegener’s granulomatosis, Churg-Strauss syndrome, Henoch-Schönlein purpura
Goodpasture’s syndrome
Trauma (needle Bx, foreign body, right-sided heart catheterization, prolonged and severe cough)
Cystic fibrosis, bullous emphysema
Pulmonary sequestration
Pulmonary arteriovenous fistula
Idiopathic pulmonary hemosiderosis
Drugs: ASA, anticoagulants, penicillamine
Pulmonary HTN
Mediastinal fibrosis

Other
Epistaxis, trauma
Laryngeal bleeding (laryngitis, laryngeal neoplasm)
Hematologic disorders (clotting abnormalities, disseminated intravascular coagulation, thrombocytopenia)

97 HEPATIC COMA
Delirium secondary to medications or illicit drugs
CVA, subdural hematoma
Meningitis, encephalitis
Hypoglycemia
Uremia
Cerebral anoxia
Hypercalcemia
Metastatic neoplasm to brain
Alcohol withdrawal syndrome

98 HEPATIC CYSTS
Congenital Hepatic Cysts
Parenchymal: solitary cyst, polycystic disease
Ductal: localized dilatation, multiple cystic dilatations of intrahepatic ducts (Caroli’s disease)

Acquired Hepatic Cysts
Inflammatory cysts: retention cysts, echinococcal cyst, amebic cyst
Neoplastic cyst
Peliosis hepatis

99 HEPATIC GRANULOMAS
Infections
Bacterial, spirochetal: tuberculosis and atypical mycobacterial infections, tularemia, brucellosis,
leprosy, syphilis, Whipple’s disease, listeriosis
Viral: mononucleosis, CMV
Rickettsial: Q fever
Fungal: coccidioidomycosis, histoplasmosis, cryptococcal infections, actinomycosis, aspergillosis, nocardiosis
Parasitic: schistosomiasis, clonorchiasis, toxocariasis, ascariasis, toxoplasmosis, amebiasis

Hepatobiliary Disorders
PBC, granulomatous hepatitis, jejunoileal bypass

Systemic Disorders
Sarcoidosis, Wegener’s granulomatosis, inflammatory bowel disease, Hodgkin’s disease, lymphoma

Drugs/Toxins
Beryllium, parenteral foreign material (e.g., starch, talc, silicone), phenylbutazone, α-methyldopa, procainamide, allopurinol, phenytoin, nitrofurantoin, hydralazine

100 HEPATOMEGALY
Frequent Jaundice
Infectious hepatitis
Toxic hepatitis
Carcinoma: liver, pancreas, bile ducts, metastatic neoplasm to liver
Cirrhosis
Obstruction of CBD
Alcoholic hepatitis
Biliary cirrhosis
Cholangitis
Hemochromatosis w/cirrhosis

Infrequent Jaundice
CHF
Amyloidosis
Liver abscess
Sarcoidosis
Infectious mononucleosis
Alcoholic fatty infiltration
Nonalcoholic steatohepatitis
Lymphoma
Leukemia
Budd-Chiari syndrome
Myelofibrosis w/myeloid metaplasia
Familial hyperlipoproteinemia type I
Other: amebiasis, hydatid disease of liver, schistosomiasis, kala-azar (Leishmania donovani infection), Hurler’s syndrome, Gaucher’s disease, kwashiorkor
Chapter 2  The Differential Diagnosis: Zebras or Horses?

101 HIRSUTISM
Idiopathic: familial, possibly ↑ sensitivity to androgens
Menopause
Polycystic ovarian syndrome
Drugs: androgens, anabolic steroids, methyltestosterone, minoxidil, diazoxide, phenytoin, glucocorticoids, cyclosporine
Congenital adrenal hyperplasia
Adrenal virilizing tumor
Ovarian virilizing tumor: arrhenoblastoma, hilus cell tumor
Pituitary adenoma
Cushing’s syndrome
Hypothyroidism (congenital and juvenile)
Acromegaly
Testicular feminization
Obesity

102 HOARSENESS
Allergic rhinitis
Infections (laryngitis, epiglottitis, tracheitis, croup, tuberculosis)
Vocal cord polyps
Voice strain
Irritants (tobacco smoke)
Vocal cord trauma (intubation, surgery)
Neoplastic involvement of vocal cord (primary or metastatic)
Neurologic abnormalities (MS, amyotrophic lateral sclerosis, parkinsonism)
Endocrine abnormalities (puberty, menopause, hypothyroidism)
Other (laryngeal webs or cysts, psychogenic, muscle tension abnormalities)

103 HYDROCEPHALUS
Head trauma
Brain neoplasm (primary or metastatic)
Spinal cord tumor
Cerebellar infarction
Exudative or granulomatous meningitis
Cerebellar hemorrhage
Subarachnoid hemorrhage
Aqueductal stenosis
Third ventricle colloid cyst
Hindbrain malformation
Viral encephalitis
Mets to leptomeninges
NPH

104 HYDRONEPHROSIS
Urinary stones
Neoplastic disease
Prostatic hypertrophy
Neurologic disease
Urinary reflux
UTI
Medication effects
Trauma
Congenital abnormality of urinary tract
Foley catheter dysfunction
Retroperitoneal fibrosis

105 HYPERCAPNIA, PERSISTENT
Hypercapnia w/nl lungs: CNS disturbances (CVA, parkinsonism, encephalitis), metabolic alkalosis, myxedema, primary alveolar hypoventilation, spinal cord lesions
Diseases of the chest wall (e.g., kyphoscoliosis, ankylosing spondylitis)
Neuromuscular disorders (e.g., myasthenia gravis, GBS, amyotrophic lateral sclerosis, muscular dystrophy, poliomyelitis)
COPD
Obesity hypoventilation syndrome

106 HYPERPIGMENTATION
Pregnancy
Drug induced (i.e., antimalarials, melanotropic hormone injection, cytotoxic agents)
PUVA therapy (psoralen administration) for psoriasis and vitiligo
Addison’s disease
ACTH- or MSH-producing tumors (e.g., oat cell carcinoma of the lung)
Hemochromatosis (“bronze” diabetes)
Malabsorption syndrome (Whipple’s disease and celiac sprue)
Melanoma
Pheochromocytoma
Porphyrias (porphyria cutanea tarda and variegate porphyria)
Progressive systemic sclerosis and related conditions
Arsenic ingestion

107 HYPERTROPHIC OSTEOARTHROPATHY
Paget’s disease
Reiter’s syndrome
Psoriasis
Osteoarthritis
RA
Osteomyelitis

108 HYPERVENTILATION, PERSISTENT
Fibrotic lung disease
Metabolic acidosis (e.g., diabetes, uremia)
CNS disorders (midbrain and pontine lesions)
Hepatic coma
Salicylate intoxication
Fever
Sepsis
Psychogenic (e.g., anxiety)
Pain from any cause

109 HYPOCAPNIA
Hyperventilation
Pneumonia, pneumonitis
Fever, sepsis
Medications (salicylates, β-adrenergic agonists, progestosterone, methylxanthines)
Pulmonary disease (asthma, interstitial fibrosis)
PE
Hepatic failure
Metabolic acidosis
High altitude
CHF
Pregnancy
Pain
CNS lesions
Hypoxemia

110 HYPOGONADISM
Hypergonadotropic Hypogonadism
Hormone resistance (androgen, luteinizing hormone insensitivity)
Gonadal defects (e.g., Klinefelter’s syndrome, myotonic dystrophy)
Drug induced (e.g., spironolactone, cytotoxins)
Alcoholism or radiation induced
Mumps orchitis
Anatomic defects, castration

Hypogonadotropic Hypogonadism
Pituitary lesions (neoplasms, granulomas, infarction, hemochromatosis, vasculitis)
Drug induced (e.g., glucocorticoids)
Hyperprolactinemia
Genetic disorders (Laurence-Moon-Biedl syndrome, Prader-Willi)
Delayed puberty
Other: chronic disease, nutritional deficiency, Kallmann’s syndrome, idiopathic isolated luteinizing hormone or FSH deficiency

111 HYPOPIGMENTATION
Vitiligo
Tinea versicolor
Atopic dermatitis
Chemical leukoderma
Idiopathic hypomelanosis
Sarcoidosis
SLE
Scleroderma
Oculocutaneous albinism
Phenylketonuria
Nevoid hypopigmentation

112 HYPTENSION, POSTURAL
Antihypertensive medications (especially α-blockers, diuretics, ACEIs)
Volume depletion (hemorrhage, dehydration)
Impaired CO (constrictive pericarditis, AS, cardiac tamponade)
Peripheral autonomic dysfunction (DM, GBS)
Idiopathic orthostatic hypotension
Central autonomic dysfunction (Shy-Drager syndrome)
Peripheral venous disease
Adrenal insufficiency

113 ISCHEMIC COLITIS, NONOCCLUSIVE
Acute Diminution of Colonic Intramural Blood Flow
Small-vessel obstruction
Collagen-vascular disease
Vasculitis, diabetes
Oral contraceptives
Nonocclusive hypoperfusion
Hemorrhage
CHF, MI, arrhythmias
Sepsis
Vasoconstricting agents: vasopressin, ergot, ephedrine, pseudoephedrine, phenylephrine
↑ Viscosity: polycythemia, sickle cell disease, thrombocytosis

Increased Demand on Marginal Blood Flow
↑ Motility
Mass lesion, stricture
Constipation
↑ Intraluminal pressure
Bowel obstruction
Colonoscopy
Barium enema

114 ISCHEMIC NECROSIS OF CARTILAGE AND BONE
Endocrine/metabolic
Ethanol abuse
Glucocorticoid therapy
Cushing’s disease
DM
Hyperuricemia
Osteomalacia
Hyperlipidemia
Storage diseases (e.g., Gaucher’s disease)
Hemoglobinopathies (e.g., sickle cell disease)
Trauma (e.g., dislocation, fracture)
HIV infection
Dysbaric conditions (e.g., caisson disease)
Collagen-vascular disorders
Irradiation
Pancreatitis
Organ transplantation
Hemodialysis
Burns
Intravascular coagulation
Idiopathic, familial

115 JAUNDICE
Predominance of Direct (Conjugated) Bilirubin
Extrahepatic obstruction:
- Common duct abnormalities: calculi, neoplasm, stricture, cyst, sclerosing cholangitis
- Metastatic carcinoma
- Pancreatic carcinoma, pseudocyst
- Ampullary carcinoma
- Hepatocellular disease: hepatitis, cirrhosis
- Drugs: estrogens, phenothiazines, captopril, methyltestosterone, labetalol
- Cholestatic jaundice of pregnancy
- Hereditary disorders: Dubin-Johnson syndrome, Rotor’s syndrome
- Recurrent benign intrahepatic cholestasis

Predominance of Indirect (Unconjugated) Bilirubin
Hemolysis: hereditary and acquired hemolytic anemias
- Inefficient marrow production
- Impaired hepatic conjugation: chloramphenicol
- Neonatal jaundice
- Hereditary disorders: Gilbert’s syndrome, Crigler-Najjar syndrome

116 JOINT SWELLING
Trauma
Osteoarthritis
Gout
Pyogenic arthritis or infectious arthritis
Pseudogout
RA
Viral syndrome

117 JUGULAR VENOUS DISTENTION
Right-sided heart failure
Cardiac tamponade
Constrictive pericarditis
Goiter
Tension pneumothorax
Pulmonary HTN
Cardiomyopathy (restrictive)
Superior vena cava syndrome
Valsalva maneuver
Right atrial myxoma
COPD

118 LEG CRAMPS, NOCTURNAL
Diabetic neuropathy
Medications
Electrolyte abnormalities
(hypokalemia, hyponatremia, hypocalcemia, hyperkalemia, hypophosphatemia)
Respiratory alkalosis
Uremia
Hemodialysis
Peripheral nerve injury
Amyotrophic lateral sclerosis
Alcohol use
Heat cramps
Vitamin B₁₂ deficiency
Hyperthyroidism
Contractures
DVT
Hypoglycemia
Peripheral vascular insufficiency
Baker’s cyst

119 LEG ULCERS
Vascular
- Arterial: arteriosclerosis, thromboangiitis obliterans, arteriovenous malformation, cholesterol emboli
- Venous: superficial varicosities, incompetent perforators, deep venous thrombosis, lymphatic abnormalities

Vasculitis, Hematologic
Sickle cell anemia, thalassemia, PV, leukemia, cold agglutinin disease
Macroglobulinemia, protein C and protein S deficiency, cryoglobulinemia, lupus anticoagulant, antiphospholipid syndrome

Infectious
Fungus: blastomycosis, coccidioidomycosis, histoplasmosis, sporotrichosis
Bacterial: furuncle, ecthyma, septic emboli
Protozoal: leishmaniasis

Metabolic
Necrobiosis lipoidica diabeticorum
Localized bullous pemphigoid
**Chapter 2  The Differential Diagnosis: Zebras or Horses?**

**Gout, calcinosis cutis, Gaucher's disease**

**Tumors**
Basal cell carcinoma, squamous cell carcinoma, melanoma
Mycosis fungoides, Kaposi's sarcoma, metastatic neoplasms

**Trauma**
Burns, cold injury, radiation dermatitis
Insect bites
Factitial, excessive pressure

**Neuropathic**
Diabetic trophic ulcers
Tabes dorsalis, syringomyelia

**Drugs**
Warfarin, intravenous colchicine
extravasation, methotrexate, halogens, ergotism, hydroxyurea

**Panniculitis**
Weber-Christian disease
Pancreatic fat necrosis, alpha-antitrypsin deficiency

**LEUKOCORIA**

Cataract
Retinal detachment
Retinoblastoma
Retinal telangiectasia
Retrolenticular vascularized membrane
Familial exudative vitreoretinopathy
Toxocariasis, retinal telangiectasia, retinopathy of prematurity

**LIVEDO RETICULARIS**

Emboli (subacute bacterial endocarditis, left atrial myxoma, cholesterol emboli)
Thrombocytopenia or polycythemia
Antiphospholipid Ab syndrome
Cryoglobulinemia, cryofibrinogenemia
Leukocytoclastic vasculitis
SLE, RA, dermatomyositis
Pancreatitis
Drugs (quinine, quinidine, amantadine, catecholamines)
Physiologic (cutis marmorata)
Congenital

**LYMPHADENOPATHY**

**Generalized**
AIDS
Lymphoma: Hodgkin's disease, non-Hodgkin's lymphoma
Leukemias, reticuloendotheliosis
Infectious mononucleosis, CMV and other viral infections
Diffuse skin infection: generalized furunculosis, multiple tick bites
Parasitic infections: toxoplasmosis, filariasis, leishmaniasis, Chagas' disease
Serum sickness
Collagen-vascular diseases (RA, SLE)
Dengue (arbovirus infection)
Sarcoidosis and other granulomatous diseases
Drugs: isoniazid, hydantoin derivatives, antithyroid and antileprosy drugs
Secondary syphilis
Hyperthyroidism, lipid storage diseases

**Localized**

Cervical nodes
Infections of the head, neck, ears, sinuses, scalp, pharynx
Mononucleosis
Lymphoma
Tuberculosis
Malignant neoplasm of head and neck
Rubella
Scalene/supraclavicular nodes
Lymphoma
Lung neoplasm
Bacterial or fungal infection of thorax or retroperitoneum
GI malignant neoplasm
Axillary nodes
Infections of hands and arms
Cat-scratch disease
Neoplasm (lymphoma, melanoma, breast carcinoma)
Brucellosis
Epitrochlear nodes
Infections of the hand
Lymphoma
Tularemia
Sarcoidosis, secondary syphilis (usually bilateral)

Inguinal nodes
Infections of leg or foot, folliculitis (pubic hair)
Lymphogranuloma venereum, syphilis
Lymphoma
Pelvic malignant neoplasm
Pasturella pestis infection

Hilar nodes
Sarcoidosis
Tuberculosis
Lung carcinoma
Fungal infections, systemic

Mediastinal nodes
Sarcoidosis
Lymphoma
Lung neoplasm
Tuberculosis
Mononucleosis
Histoplasmosis
Abdominal/retroperitoneal nodes
Lymphoma
Tuberculosis
Neoplasm (ovary, testes, prostate, colon, and other malignant neoplasms)

**123 MEDIASTINAL MASSES OR WIDENING ON CHEST X-RAY**

Lymphoma: Hodgkin’s disease and non-Hodgkin’s lymphoma
Sarcoidosis
Vascular: aortic aneurysm, ectasia or tortuosity of aorta or bronchopulmonary vessels
Carcinoma: lungs, esophagus
Esophageal diverticula
Hiatal hernia
Achalasia
Prominent pulmonary outflow tract: pulmonary HTN, PE, right-to-left shunts
Trauma: mediastinal hemorrhage
Pneumomediastinum
Lymphadenopathy caused by silicosis and other pneumoconioses
Leukemias
Infections: tuberculosis, viral (rare), mycoplasmal (rare), fungal, tularemia
Subternal thyroid
Thymoma
Teratoma
Bronchogenic cyst
Pericardial cyst
Neurofibroma, neurosarcoma, ganglioneuroma

**124 MESENTERIC ISCHEMIA, NONOCCLUSIVE**

CV disease resulting in low-flow states (CHF, cardiogenic shock, post cardiopulmonary bypass, dysrhythmias)
Septic shock
Drug induced (cocaine, vasopressors, ergot alkaloid poisoning)

**125 MESENTERIC VENOUS THROMBOSIS**

Hypercoagulable states (protein C or S deficiency, antithrombin III deficiency, factor V Leyden, malignant neoplasm, PV, sickle cell disease, homocystinemia, lupus anticoagulant, cardiolipin Ab)
Trauma (operative venous injury, abdominal trauma, post splenectomy)

Inflammatory conditions (pancreatitis, diverticulitis, appendicitis, cholangitis)
Other: CHF, renal failure, portal HTN, decompression sickness

**126 METASTATIC NEOPLASMS**

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<td>Choriocarcinoma</td>
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**127 MIOSIS**

Medications (e.g., morphine, pilocarpine)
Neurosyphilis
Congenital Iritis
CNS pontine lesion
CNS infections
Cavernous sinus thrombosis
Inflammation/irritation of cornea or conjunctiva

**128 MONONEUROPATHY**

Herpes zoster
Herpes simplex
Vasculitis
Trauma, compression
Diabetes
Postinfectious or inflammatory Lyme disease

**129 MUSCLE WEAKNESS**

Physical deconditioning
Impaired CO (e.g., mitral stenosis, MR, CHF)
Uremia, liver failure
Electrolyte abnormalities (hypokalemia, hyperkalemia, hypophosphatemia, hypercalcemia), hypoglycemia
Drug induced (e.g., statin myopathy)
Muscular dystrophies
Steroid myopathy
Alcoholic myopathy
Myasthenia gravis, Lambert-Eaton syndrome
Infections (polio, botulism, HIV infection, hepatitis, diphtheria, tick paralysis, neurosyphilis, brucellosis, tuberculosis, trichinosis)
Pernicious anemia, other anemias, beriberi
Psychiatric illness (depression, somatization syndrome)
Organophosphate or arsenic poisoning
Inflammatory myopathies (e.g., collagen-vascular disease, RA, sarcoidosis)
Endocrinopathies (e.g., adrenal insufficiency, hypothyroidism), diabetic neuropathy
Other: motor neuron disease, mitochondrial myopathy, L-tryptophan (eosinophilia-myalgia), rhabdomyolysis, glycogen storage disease, lipid storage disease, muscle phosphorylase deficiency

**130 MYODRIASIS**
Coma
Medications (cocaine, atropine, epinephrine, others)
Glaucome
Cerebral aneurysm
Ocular trauma
Head trauma
Optic atrophy
Cerebral neoplasm
Iridocyclitis

**131 MYELOPATHY AND MYELITIS**

**Inflammatory**
Infectious: spirochetal, tuberculosis, herpes zoster, rabies, HIV infection, polio, rickettsial, fungal, parasitic
Noninfectious: idiopathic transverse myelitis, MS

**Toxic/Metabolic**
DM, pernicious anemia, chronic liver disease, pellagra, arsenic

**Trauma, Compression**
Spinal neoplasm, cervical spondylosis, epidural abscess, epidural hematoma

**Vascular**
Arteriovenous malformation, SLE, PAN, dissecting aortic aneurysm

**Physical Agents**
Electrical injury, irradiation

**Neoplastic**
Spinal cord tumors, paraneoplastic myelopathy

**132 MYOPATHIES, INFECTIOUS**
HIV infection
Viral myositis
Trichinosis

Toxoplasmosis
Cysticercosis
Bacterial infections

**133 MYOPATHIES, INFLAMMATORY**
SLE, RA
Sarcoidosis
Paraneoplastic syndrome
Polymyositis, dermatomyositis
Polyarteritis nodosa
MCTD
Scleroderma
Inclusion body myositis
Sjögren’s syndrome
Cimetidine, D-penicillamine

**134 MYOTONIA**
Myotonia congenita (Thomsen’s disease)
May be autosomal dominant or recessive (two distinct varieties)
The disease is limited to muscles and causes hypertrophy and stiffness after rest. Muscle function normalizes w/exercise. There is no weakness. Symptoms are exacerbated by exposure to cold.

Paramyotonia congenita
Autosomal dominant disease
Weakness and stiffness of facial muscles and distal upper extremities, especially or exclusively on cold exposure

Muscular dystrophies
Inflammatory myopathies (polymyositis)
Metabolic muscle diseases
Myasthenic syndromes
Motor neuron disease

**135 NAIL CLUBBING**
COPD
Pulmonary malignant neoplasm
Cirrhosis
IBD
Chronic bronchitis
CHD
Endocarditis
AV malformations
Asbestosis
Trauma
Idiopathic

**136 NAUSEA AND VOMITING**
Infections (viral, bacterial)
Intestinal obstruction
Metabolic (uremia, electrolyte abnormalities, DKA, acidosis, others)
Severe pain
Anxiety, fear
Psychiatric disorders (bulimia, anorexia nervosa)
Pregnancy
Medications (NSAIDs, erythromycin, morphine, codeine, aminophylline, chemotherapeutic agents, others)
Withdrawal from substance abuse (drugs, alcohol)
Head trauma
Vestibular or middle ear disease
Migraine headache
CNS neoplasms
Radiation sickness
PUD
Carcinoma of GI tract
Reye’s syndrome
Eye disorders
Abdominal trauma

**137 NECK MASS**

**Congenital Anomalies**
Thyroglossal duct cyst
Bronchial apparatus anomalies
Teratomas
Ranula
Dermoid cysts
Hemangioma
Laryngoceles
Cystic hygroma

**Non-Neoplastic Inflammatory Etiologies**
Folliculitis
Adenopathy secondary to peritonsillar abscess
Retropharyngeal or parapharyngeal abscess
Salivary gland infections
Viral infections (mononucleosis, HIV, CMV)
Tuberculosis
Cat-scratch disease
Toxoplasmosis
*Actinomyces*
Atypical mycobacterium
Jugular vein thrombus
Neoplasm (primary or metastatic)
Lipoma

**138 NYSTAGMUS**
Medications (meperidine, barbiturates, phenytoin, phenothiazines, others)
MS
Congenital
Neoplasm (cerebellar, brainstem, cerebral)
Labyrinthine or vestibular lesions (otoliths)
CNS infections

Optic atrophy
Other: Arnold-Chiari malformation, syringobulbia, chorioretinitis, meningeal cysts

**139 OPHTHALMOPLEGIA**

**Bilateral**
Botulism
Myasthenia gravis
Wernicke’s encephalopathy
Acute cranial polyneuropathy
Brainstem stroke

**Unilateral**
Carotid—posterior (third cranial nerve, pupil involved, communicating aneurysm)
Diabetic—idiopathic (third or sixth cranial nerve, pupil spared)
Myasthenia gravis
Brainstem stroke

**140 PALPITATIONS**
Anxiety
Electrolyte abnormalities (hypokalemia, hypomagnesemia)
Exercise
Hyperthyroidism
Ischemic heart disease
Ingestion of stimulant drugs (cocaine, amphetamines, caffeine)
Medications (digoxin, β-blockers, Ca channel antagonists, hydralazines, diuretics, minoxidil)
Hypoglycemia
MVP
WPW syndrome
SSS
AF

**141 PAPILLEDEMA**
CNS infections (viral, bacterial, fungal)
Medications (lithium, cisplatin, corticosteroids, tetracycline, others)
Head trauma
CNS neoplasm (primary or metastatic)
Pseudotumor cerebri
Cavernous sinus thrombosis
SLE
Sarcoidosis
Subarachnoid hemorrhage
Carbon dioxide retention
Arnold-Chiari malformation and other developmental or congenital malformations
Orbital lesions
Central retinal vein occlusion
Hypertensive encephalopathy
Metabolic abnormalities
Chapter 2  The Differential Diagnosis: Zebras or Horses?

142 PARAPLEGIA
Trauma: penetrating wounds to motor cortex, fracture-dislocation of vertebral column w/ compression of spinal cord or cauda equina, prolapsed disk, electrical injuries
Neoplasm: parasagittal region, vertebrae, meninges, spinal cord, cauda equina, Hodgkin’s disease, non-Hodgkin’s lymphoma, leukemic deposits, pelvic neoplasms
MS and other demyelinating disorders
Mechanical compression of spinal cord, cauda equina, or lumbosacral plexus: Paget’s disease, kyphoscoliosis, herniation of intervertebral disk, spondylitis, ankylosing spondylitis, RA, aortic aneurysm
Infections: spinal abscess, syphilis, tuberculous, poliomyelitis, leprosy
Thrombosis of superior sagittal sinus
Polyneuritis: GBS, diabetes, alcohol, beriberi, heavy metals
Heredofamilial muscular dystrophies
Amyotrophic lateral sclerosis
Congenital and familial conditions: syringomyelia, myelomenigocele, myelodysplasia
Hysteria

143 PARESTHESIAS
MS
Nutritional deficiencies (thiamine, vitamin B12, folic acid)
Compression of spinal cord or peripheral nerves
Medications (e.g., isoniazid, lithium, nitrofurantoin, gold, cisplatin, hydralazine, amitriptyline, sulfonamides, amiodarone, metronidazole, dapsone, disulfiram, chloramphenicol)
Toxic chemicals (e.g., lead, arsenic, cyanide, mercury, organophosphates)
DM
Myxedema
Alcohol
Sarcoidosis
Neoplasms
Infections (HIV, Lyme disease, herpes zoster, leprosy, diphtheria)
Charcot-Marie-Tooth syndrome and other hereditary neuropathies
Guillain-Barré neuropathy

144 PELVIC MASS
Hemorrhagic ovarian cyst
Simple ovarian cyst (follicle or corpus luteum)
Ovarian carcinoma, carcinoma of fallopian tube, colorectal carcinoma, metastatic carcinoma, prostate carcinoma, bladder carcinoma, lymphoma, Hodgkin’s disease
Cystadenoma, teratoma, endometrioma
Leiomyoma
Leiomyosarcoma
Diverticulitis, diverticular abscess
Appendiceal abscess, tubo-ovarian abscess
Ectopic pregnancy, intrauterine pregnancy
Paraovarian cyst
Hydrosalpinx

145 PERICARDIAL EFFUSION
Pericarditis (viral, tuberculous, bacterial, idiopathic)
Uremia
Myxedema
Neoplasm (leukemia, lymphoma, metastatic)
Hemorrhage (trauma, leakage of thoracic aneurysm)
SLE, rheumatoid disease
MI and post cardiac surgery
Dressler’s syndrome

146 PLEURAL EFFUSIONS
Exudative
Neoplasm: bronchogenic carcinoma, breast carcinoma, mesothelioma, lymphoma, ovarian carcinoma, MM, leukemia, Meigs’ syndrome
Infections: viral pneumonia, bacterial pneumonia, Mycoplasma infection, tuberculosis, fungal and parasitic diseases, extension from subphrenic abscess
Trauma
Collagen-vascular diseases: SLE, RA, scleroderma, polyarteritis, Wegener’s granulomatosis
Pulmonary infarction
Pancreatitis
Post cardiomyotomy/Dressler’s syndrome
Drug-induced lupus erythematosus (hydralazine, procainamide)
Post abdominal surgery
Ruptured esophagus
Chronic effusion secondary to congestive failure
Chapter 2  The Differential Diagnosis: Zebras or Horses?  127

Transudative
CHF
Hepatic cirrhosis
Nephrotic syndrome
Hypoproteinemia from any cause
Meigs’ syndrome

**147 PNEUMONIA, RECURRENT**

Mechanical obstruction from neoplasm
Chronic aspiration (tube feeding, alcoholism, CVA, neuromuscular disorders, seizure disorder, inability to cough)
Bronchiectasis
Kyphoscoliosis
COPD, CHF, asthma, silicosis, pulmonary fibrosis, cystic fibrosis
Pulmonary tuberculosis, chronic sinusitis
Immunosuppression (HIV infection, corticosteroids, leukemia, chemotherapy, splenectomy)

**148 POLYNEUROPATHY, SYMMETRIC**

Acquired Neuropathies
Toxic
Drugs
Industrial toxins
Heavy metals
Abused substances
Metabolic/endocrine
Diabetes
Chronic renal failure
Hypothyroidism
Polyneuropathy of critical illness
Nutritional deficiency
Vitamin B₁₂ deficiency
Alcoholism
Vitamin E deficiency
Paraneoplastic
Carcinoma
Lymphoma
Plasma cell dyscrasia
Myeloma, typical, atypical, and solitary forms
Primary systemic amyloidosis

Inherited Neuropathies
Neuropathies w/biochemical markers
Refsum’s disease
Bassen-Kornzweig disease
Tangier disease
Metachromatic leukodystrophy
Krabbe’s disease
Adrenomyeloneuropathy
Fabry’s disease
Neuropathies w/o biochemical markers or systemic involvement
Hereditary motor neuropathy
Hereditary sensory neuropathy
Hereditary sensorimotor neuropathy

Other
Idiopathic chronic inflammatory demyelinating polyneuropathies
Polyneuropathies associated w/ peripheral nerve autoantibodies
AIDS

**149 POLYURIA**

DM
Diabetes insipidus
Primary polydipsia (compulsive water drinking)
Hypercalcemia
Hypokalemia
Post obstructive uropathy
Diuretic phase of ARF (specifically ATN)
Drugs: diuretics, caffeine, alcohol, lithium
Sickle cell trait or disease, chronic pyelonephritis (failure to concentrate urine)
Anxiety, cold weather

**150 POPLITEAL SWELLING**

Phlebitis (superficial)
Lymphadenitis
Trauma: fractured tibia or fibula, contusion, traumatic neuroma
DVT
Ruptured varicose vein
Baker’s cyst
Popliteal abscess
Osteomyelitis
Ruptured tendon
Aneurysm of popliteal artery
Neoplasm: lipoma, osteogenic sarcoma, neurofibroma, fibrosarcoma

**151 PORTAL HYPERTENSION**

Increased Resistance to Flow
Presinusoidal
Portal or splenic vein occlusion (thrombosis, tumor)
Schistosomiasis
Congenital hepatic fibrosis
Sarcoidosis
Sinusoidal
Cirrhosis (all causes)
Alcoholic hepatitis
Postsinusoidal
Venocclusive disease
Budd-Chiari syndrome
Constrictive pericarditis (or severe right-sided heart failure from any cause)
Chapter 2  The Differential Diagnosis: Zebras or Horses?

Increased Portal Blood Flow
Splenomegaly not due to liver disease
Arterioportal fistula

152 POSTMENOPAUSAL BLEEDING
Hormone replacement therapy
Neoplasm (uterine, ovarian, cervical, vaginal, vulvar)
Atrophic vaginitis
Vaginal infection
Polyp
Extragenital (GI, urinary)
Tamoxifen
Trauma

153 PROPTOSIS
Thyrotoxicosis
Orbital pseudotumor
Optic nerve tumor
Cavernous sinus arteriovenous fistula, cavernous sinus thrombosis
Cellulitis
Metastatic tumor to orbit

154 PROTEINURIA
Nephrotic syndrome as a result of primary renal diseases
Malignant HTN
Malignant diseases: MM, leukemias, Hodgkin’s disease
CHF
DM
SLE, RA
Sickle cell disease
Goodpasture’s syndrome
Malaria
Amyloidosis, sarcoidosis
Tubular lesions: cystinosis
Functional (after heavy exercise)
Pyelonephritis
Pregnancy
Constrictive pericarditis
Renal vein thrombosis
Toxic nephropathies: heavy metals, drugs
Radiation nephritis
Orthostatic (postural) proteinuria
Benign proteinuria: fever, heat, or cold exposure

155 PRURITUS
Dry skin
Drug-induced eruption, fiberglass exposure
Scabies
Skin diseases
Myeloproliferative disorders: mycosis fungoides, Hodgkin’s lymphoma, MM, PV
Cholestatic liver disease
Endocrine disorders: DM, thyroid disease, carcinoid, pregnancy
Carcinoma: breast, lung, gastric
Chronic renal failure
Iron deficiency
AIDS
Neurosis
Sjögren’s syndrome

156 PRURITUS ANI
Fecal irritation:
Poor hygiene
Anorectal conditions (fissure, fistula, hemorrhoids, skin tags, perianal clefts)
Spicy foods, citrus foods, caffeine, colchicine, quinidine
Contact dermatitis: anesthetic agents, topical corticosteroids, perfumed soap
Dermatologic disorders: psoriasis, seborrhea, lichen simplex or sclerous
Systemic disorders: chronic renal failure, myxedema, DM, thyrotoxicosis, PV, Hodgkin’s disease
STDs: syphilis, HSV, HPV
Other infectious agents: pinworms, scabies
Bacterial infection, viral infection

157 PSEUDOMIOLARITY
Lead placement
Normal variant
Poor R wave progression
Chest deformity
Trauma to chest, pneumothorax
Cardiomyopathy
COPD
Hyperkalemia
Left anterior fascicular block
Left BBB
LVH
Myocarditis and pericarditis
PE
WPW syndrome
Chagas’ disease
Rare causes: cardiac tumors, pancreatitis, amyloidosis, sarcoidosis, scleroderma, HIV infection

158 PTOSIS
Third nerve palsy
Myasthenia gravis
Horner’s syndrome
Senile ptosis

159 PULMONARY CRACKLES
Pneumonia
Left ventricular failure
Asbestosis, silicosis, ILD
Chronic bronchitis
Chapter 2  The Differential Diagnosis: Zebras or Horses?

160 PULMONARY LESIONS

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Legionella pneumonia</td>
</tr>
<tr>
<td>Mycoplasma pneumonia</td>
</tr>
<tr>
<td>Viral pneumonia</td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td>Pneumocystis carinii pneumonia</td>
</tr>
<tr>
<td>Hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Aspiration pneumonia</td>
</tr>
<tr>
<td>Fungal disease (aspergillosis, histoplasmosis)</td>
</tr>
<tr>
<td>ARDS associated w/pneumonia</td>
</tr>
<tr>
<td>Psittacosis</td>
</tr>
<tr>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Septic emboli</td>
</tr>
<tr>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Multiple pulmonary emboli</td>
</tr>
<tr>
<td>Rheumatoid nodules</td>
</tr>
</tbody>
</table>

161 PULMONARY NODULE, SOLITARY

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Granuloma from histoplasmosis</td>
</tr>
<tr>
<td>Tuberculosis granuloma</td>
</tr>
<tr>
<td>Granuloma from coccidioidomycosis</td>
</tr>
<tr>
<td>Metastatic carcinoma</td>
</tr>
<tr>
<td>Bronchial adenoma</td>
</tr>
<tr>
<td>Bronchogenic cyst</td>
</tr>
<tr>
<td>Hamartoma</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
</tr>
<tr>
<td>Other: fibroma, intrapulmonary lymph node, sclerosing hemangioma, bronchopulmonary sequestration</td>
</tr>
</tbody>
</table>

162 PURPURA

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Septic emboli, atheromatous (cholesterol) emboli</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Meningococcemia</td>
</tr>
<tr>
<td>RMSF</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
</tr>
<tr>
<td>Viral infection: echovirus, coxsackievirus</td>
</tr>
<tr>
<td>Scurvy</td>
</tr>
<tr>
<td>Other: left atrial myxoma, cryoglobulinemia, vasculitis, hyperglobulinemic purpura, leukemia, bacterial endocarditis</td>
</tr>
</tbody>
</table>

163 RECTAL PAIN

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anal fissure</td>
</tr>
<tr>
<td>Thrombosed hemorrhoid</td>
</tr>
<tr>
<td>Anorectal abscess</td>
</tr>
<tr>
<td>Foreign bodies</td>
</tr>
<tr>
<td>Fecal impaction</td>
</tr>
</tbody>
</table>

Endometriosis
Neoplasms (primary or metastatic)
PID
Inflammation of sacral nerves
Compression of sacral nerves
Prostatitis
Other: proctalgia fugax, uterine abnormalities, myopathies, coccygodynia

164 RED EYE

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious conjunctivitis (bacterial, viral)</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
</tr>
<tr>
<td>Acute glaucoma</td>
</tr>
<tr>
<td>Keratitis (bacterial, viral)</td>
</tr>
<tr>
<td>Iritis</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Foreign body</td>
</tr>
</tbody>
</table>

165 RENAL ARTERY OCCLUSION, CAUSES

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
</tr>
<tr>
<td>Angiography or stent placement</td>
</tr>
<tr>
<td>Abdominal aortic surgery</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Renal artery aneurysm/dissection</td>
</tr>
<tr>
<td>Vasculitis</td>
</tr>
<tr>
<td>Thrombosis in patient w/fibromuscular dysplasia</td>
</tr>
<tr>
<td>Atherosclerosis</td>
</tr>
<tr>
<td>Septic embolism</td>
</tr>
<tr>
<td>Mural thrombus thromboembolism</td>
</tr>
<tr>
<td>Atrial myxoma thromboembolism</td>
</tr>
<tr>
<td>Mitral stenosis thromboembolism</td>
</tr>
<tr>
<td>Prosthetic valve thromboembolism</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Marantic endocarditis</td>
</tr>
<tr>
<td>Dissection/rupture of AAA</td>
</tr>
</tbody>
</table>

166 SCROTAL SWELLING

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocele</td>
</tr>
<tr>
<td>Varicocele</td>
</tr>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>Acute epididymitis</td>
</tr>
<tr>
<td>Orchitis</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Hernia</td>
</tr>
<tr>
<td>Torsion of spermatic cord</td>
</tr>
<tr>
<td>Torsion of epididymitis</td>
</tr>
<tr>
<td>Torsion of testis</td>
</tr>
<tr>
<td>Insect bite</td>
</tr>
<tr>
<td>Folliculitis</td>
</tr>
<tr>
<td>Sebaceous cyst</td>
</tr>
<tr>
<td>Thrombosis of spermatic vein</td>
</tr>
<tr>
<td>Other: lymphedema, dermatitis, fat necrosis, Henoch-Schönlein purpura, idiopathic scrotal edema</td>
</tr>
</tbody>
</table>

167 SEIZURE

<table>
<thead>
<tr>
<th>Disease/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
</tr>
<tr>
<td>Alcohol abuse/withdrawal</td>
</tr>
<tr>
<td>TIA</td>
</tr>
</tbody>
</table>
Hemiparetic migraine
Psychiatric disorders
Carotid sinus hypersensitivity
Hyperventilation, prolonged breath holding
Hypoglycemia
Narcolepsy
Movement disorders (tics, hemiballismus)
Hyponatremia
Brain tumor (primary or metastatic)
Tetanus
Strychnine, phencyclidine poisoning
Epilepsy
Cerebral anoxia from any cause

### 168 SHOULDER PAIN

#### With Local Findings in Shoulder

<table>
<thead>
<tr>
<th>Trauma: contusion, fracture, muscle strain, trauma to spinal cord</th>
<th>Arthritis, arthritis, RA, ankylosing spondylitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bursitis, synovitis, tendinitis, tenosynovitis</td>
<td>Aseptic (avascular) necrosis</td>
</tr>
<tr>
<td>Local infection: septic arthritis, osteomyelitis, abscess, herpes zoster, tuberculosis</td>
<td></td>
</tr>
</tbody>
</table>

#### Without Local Findings in Shoulder

<table>
<thead>
<tr>
<th>CV disorders: ischemic heart disease, pericarditis, aortic aneurysm</th>
<th>Subdiaphragmatic abscess, liver abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholelithiasis, cholecystitis</td>
<td>Subphrenic abscess</td>
</tr>
<tr>
<td>Pulmonary lesions: apical bronchial carcinoma, pleurisy, pneumonothorax, pneumonia</td>
<td></td>
</tr>
<tr>
<td>GI lesions: PUD, gastric neoplasm, peptic esophagitis</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Pancreatic lesions: carcinoma, calculi, pancreatitis</td>
<td>Gallstones</td>
</tr>
<tr>
<td>CNS abnormalities: neoplasm, vascular abnormalities</td>
<td>Barium</td>
</tr>
<tr>
<td>MS</td>
<td></td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>Spinal cord AV malformations</td>
</tr>
<tr>
<td>Polymyositis/dermatomyositis</td>
<td>Adrenoleukodystrophy</td>
</tr>
<tr>
<td>Psychogenic</td>
<td></td>
</tr>
<tr>
<td>Polymyalgia rheumatic</td>
<td></td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td></td>
</tr>
</tbody>
</table>

### 169 SMALL BOWEL OBSTRUCTION

#### Intrinsic

<table>
<thead>
<tr>
<th>Congenital (atresia, stenosis)</th>
<th>Inflammatory (Crohn’s, radiation enteritis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplasms (metastatic or primary)</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Traumatic (hematoma)</td>
<td></td>
</tr>
</tbody>
</table>

#### Extrinsic

<table>
<thead>
<tr>
<th>Hernias (internal and external)</th>
<th>Adhesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volvulus</td>
<td>Compressing masses (tumors, abscesses, hematomas)</td>
</tr>
</tbody>
</table>

### 170 INTRALUMINAL

<table>
<thead>
<tr>
<th>Foreign body</th>
<th>Gallstones</th>
<th>Bezoars</th>
<th>Barium</th>
<th>Ascaris infestation</th>
</tr>
</thead>
</table>

### 171 SPASIC PARAPLEGIAS

<table>
<thead>
<tr>
<th>Cervical spondylosis</th>
<th>Friedreich’s ataxia</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>Spinal cord tumor</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Tertiary syphilis</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
<td>Spino-cerebellar ataxias</td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>Spinal cord AV malformations</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td></td>
</tr>
</tbody>
</table>

### 172 SPINAL CORD DYSFUNCTION

<table>
<thead>
<tr>
<th>Trauma</th>
<th>MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse myelitis</td>
<td>Neoplasm (primary, metastatic)</td>
</tr>
<tr>
<td>Syringomyelia</td>
<td>Spinal epidural abscess</td>
</tr>
<tr>
<td>HIV myelopathy</td>
<td>Diskitis</td>
</tr>
<tr>
<td>Spinal epidural hematoma</td>
<td>Spinal cord infarction</td>
</tr>
<tr>
<td>Spinal AV malformation</td>
<td>Subarachnoid hemorrhage</td>
</tr>
</tbody>
</table>

### 173 SPLENOMEGALY

<table>
<thead>
<tr>
<th>Hepatic cirrhosis</th>
<th>Neoplastic involvement: chronic myelogenous leukemia, CLL, lymphoma, MM</th>
</tr>
</thead>
</table>
Bacterial infections: tuberculosis, infectious endocarditis, typhoid fever, splenic abscess
Viral infections: infectious mononucleosis, viral hepatitis, HIV infection
Gaucher’s disease and other lipid storage diseases
Sarcoidosis
Parasitic infections (malaria, kala-azar, histoplasmosis)
Hereditary and acquired hemolytic anemias
Idiopathic thrombocytopenic purpura
Collagen-vascular disorders: SLE, RA (Felt’s syndrome), polyarteritis nodosa
Serum sickness, drug hypersensitivity reaction
Splenic cysts and benign tumors: hemangioma, lymphangioma
Thrombosis of splenic or portal vein
PV, myeloid metaplasia

**174 SPONDYLOARTHRITIDES (SPONDYLARTHRITIDIES, SERONEGATIVE ARTHRITIS SYNDROMES)**

Definition: seronegative arthritis syndromes characterized clinically by back pain, extra-articular disorders, and peripheral arthritis. These disorders show familial aggregation and are typically associated w/HLA genes of the major histocompatibility complex, particularly HLA-B27.

Ankylosing spondylitis
Reiter’s syndrome
Psoriatic arthritis
Arthritis associated w/GI disease

**175 STEATOHEPATITIS**

Alcohol abuse
Obesity
DM
Parenteral nutrition
Medications (high-dose estrogen, amiodarone, corticosteroids, methotrexate, nifedipine)

Jejunoileal bypass
Abetalipoproteinemia
Wilson’s disease, Weber-Christian disease

**176 STROKE**

Hypoglycemia
Drug OD or intoxication
Hysterical conversion reaction
Hyperventilation
Metabolic encephalopathy
Migraine

Syncope
Transient global amnesia
Seizures (postictal)
Vestibular vertigo

**177 STROKE, YOUNG ADULT, CAUSES**

Cardiac factors (ASD, MVP, patent foramen ovale)
Inflammatory factors (SLE, polyarteritis nodosa)
Infections (endocarditis, neurosyphilis)
Drugs (cocaine, heroin, oral contraceptives, decongestants)
Arterial dissection
Hematologic factors (disseminated intravascular disease, TTP, homocystinemia, lupus anticoagulant)

Migraine
Postpartum angiopathy
Others: premature atherosclerosis, fibromuscular dysplasia, sickle cell disease

**178 SWOLLEN LIMB**

Trauma
Insect bite
Abscess
Lymphedema
Thrombophlebitis
Lipoma
Neurofibroma
Postphlebitic syndrome
Myositis ossificans
Nephrosis, cirrhosis, CHF
Hypoalbuminemia
Varicose veins
DVT
Compartment syndrome
Cellulitis

**179 TARDIVE DYSKINESIA**

Medications (antidepressants, anticholinergics, amphetamines, lithium, levodopa, phenytoin)

Brain neoplasms
Huntington’s disease
Idiopathic dystonias (tics, blepharospasm, aging)
Wilson’s disease
Extrapyramidal syndrome (postanoxic or postencephalitic)
Torsion dystonia

**180 TASTE AND SMELL LOSS**

Taste
Local: radiation therapy
Systemic: cancer, renal failure, hepatic failure, nutritional
deficiency (vitamin B₁₂, zinc), Cushing’s syndrome, hypothyroidism, DM, infection (influenza), drugs (antirheumatic and antiproliferative)

Neurologic: Bell’s palsy, familial dysautonomia, MS

Smell
Local: allergic rhinitis, sinusitis, nasal polyposis, bronchial asthma
Systemic: renal failure, hepatic failure, nutritional deficiency (vitamin B₁₂), Cushing’s syndrome, hypothyroidism, DM, infection (viral hepatitis, influenza), drugs (nasal sprays, Abx)

Neurologic: head trauma, MS, Parkinson’s disease, frontal brain tumor

181 TESTICULAR PAIN
Testicular torsion
Trauma
Epididymitis
Orchitis
Neoplasm
Urolithiasis
Inguinal hernia
Infection (cellulitis, abscess, folliculitis)
Anxiety
Ruptured AAA

182 TICK-RELATED INFECTIONS
Lyme disease
RMSF
Babesiosis
Tularemia
Q fever
Colorado tick fever
Ehrlichiosis
Relapsing fever

183 TREMOR
Tremor Present at Rest
Parkinsonism
CNS neoplasms
Tardive dyskinesia

Postural Tremor (present during maintenance of a posture)
Essential senile tremor

Action Tremor (present with movement)
Anxiety
Medications (bronchodilators, caffeine, corticosteroids, lithium, others)
Endocrine disorders (hyperthyroidism, pheochromocytoma, carcinoid)
Withdrawal from substance abuse

184 URETHRAL DISCHARGE AND DYSURIA
Urethritis (gonococcal, chlamydial, trichomonal)
Cystitis
Prostatitis
Vaginitis (candidiasis, chemical)
Meatal stenosis
Interstitial cystitis
Trauma (foreign body, masturbation, horseback or bike riding)

185 URINARY RETENTION, ACUTE
Mechanical obstruction: urethral stone, foreign body, urethral stricture, benign prostatic hypertrophy, prostate carcinoma, prostatitis, trauma w/hematoma formation or obstructive clots
Neurogenic bladder
Neurologic disease (MS, parkinsonism, tabes dorsalis, CVA)
Spinal cord injury
CNS neoplasm (primary or metastatic)
Spinal anesthesia
Lower urinary tract instrumentation
Medications (antihistamines, antidepressants, narcotics, anticholinergics)
Abdominal or pelvic surgery
Alcohol toxicity
Pregnancy
Anxiety
Encephalitis
Postoperative pain
Spina bifida occulta

186 VAGINITIS
See Table 2-3.

187 VASCULITIS
See Table 2-4.

188 VERTIGO
Peripheral
Otitis media
Acute labyrinthitis
Vestibular neuronitis
Benign positional vertigo
Meniere’s disease
Ototoxic drugs: streptomycin, gentamicin
### TABLE 2-3  Differential Diagnosis of Vaginitis

<table>
<thead>
<tr>
<th>Characteristics of Vaginal Discharge</th>
<th>Characteristics of Vaginal Discharge</th>
<th>Characteristics of Vaginal Discharge</th>
<th>Characteristics of Vaginal Discharge</th>
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</thead>
<tbody>
<tr>
<td>pH</td>
<td>C. albicans Vaginitis</td>
<td>T. vaginalis Vaginitis</td>
<td>Bacterial Vaginosis</td>
</tr>
<tr>
<td>4.5</td>
<td>&gt;5.0</td>
<td>&gt;5.0</td>
<td></td>
</tr>
<tr>
<td>White curd</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Odor w/KOH</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Clue cells</td>
<td>No</td>
<td>No</td>
<td>Usually</td>
</tr>
<tr>
<td>Motile trichomonads</td>
<td>No</td>
<td>Usually</td>
<td>No</td>
</tr>
<tr>
<td>Yeast cells</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

### FIGURE 2-3. Viral hepatitis diagnostic algorithm.

Lesions of the eighth nerve: acoustic neuroma, meningioma, mononeuropathy, metastatic carcinoma
Mastoiditis

**Central Nervous System or Systemic**
Vertebrabasilar artery insufficiency
Posterior fossa tumor or other brain tumors
Infarction/hemorrhage of cerebral cortex, cerebellum, or brainstem
Basilar migraine
Metabolic: drugs, hypoxia, anemia, fever
Hypotension/severe HTN
MS
CNS infections: viral, bacterial

Temporal lobe epilepsy
Arnold-Chiari malformation, syringobulbia
Psychogenic: ventilation, hysteria

**189 VIRAL HEPATITIS**
See Figure 2-3.

**190 VISION LOSS, ACUTE, PAINFUL**
Acute angle-closure glaucoma
Corneal ulcer
Uveitis
Endophthalmitis
Factitious
Somatization syndrome
Trauma
Giant cell arteritis
### TABLE 2-4  Common Manifestations of Vasculitis

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Giant Cell Arteritis*</th>
<th>Takayasu’s Arteritis*</th>
<th>Polyarteritis Nodosa1</th>
<th>Churg-Strauss Vasculitis1</th>
<th>Wegener’s Granulomatosis1</th>
<th>Hypersensitivity Vasculitis§</th>
<th>Henoch-Schönlein Purpura1</th>
<th>Essential Cryoglobulinemia§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td></td>
<td></td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI pain</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Large-vessel granulomatous disease.
1Medium-vessel granulomatous disease.
1Small-vessel granulomatous disease.
§Leukocytoclastic vasculitis.
+, occasionally seen; ++, commonly seen; +++ , frequently seen.
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[Diagram: Visual field defects]

**Figure 2-4.** Visual field defects. A, Transection of right optic nerve: ipsilateral monocular blindness. B, Lesion of right optic tract: left homonymous hemianopia. C, Chiasmal lesion: bitemporal hemianopia. D, Lesion of left optic nerve and chiasm: ipsilateral blindness and right temporal deficit.

**191 Vision Loss, Acute, Painless**
- Retinal artery occlusion
- Optic neuritis
- Retinal vein occlusion
- Vitreous hemorrhage
- Retinal detachment
- Exudative macular degeneration
- CVA
- Ischemic optic neuropathy
- Factitious
- Somatization syndrome, anxiety reaction
- Giant cell arteritis

**192 Vision Loss, Chronic, Progressive**
- Cataract
- Macular degeneration
- Cerebral neoplasm
- Refractive error
- Open-angle glaucoma

**193 Visual Field Defects**
See Figure 2-4.

**194 Vocal Cord Paralysis**
- Neoplasm: primary or metastatic (e.g., lung, thyroid, parathyroid, mediastinum)
- Neck surgery (parathyroid, thyroid, carotid endarterectomy, cervical spine)
- Idiopathic
- Viral, bacterial, tuberculous, or fungal infection
- Trauma (intubation, penetrating neck injury)
- Cardiac surgery
- RA
- MS
- Parkinsonism
- Toxic neuropathy
- CVA
- CNS abnormalities: hydrocephalus, Arnold-Chiari malformation, meningomyelocele
Chapter 2  The Differential Diagnosis: Zebras or Horses?

195 VOMITING

GI disturbances:
- Obstruction: esophageal, pyloric, intestinal
- Infections: viral or bacterial enteritis, viral hepatitis, food poisoning, gastroenteritis
- Pancreatitis
- Appendicitis
- Biliary colic
- Peritonitis
- Perforated bowel
- Diabetic gastroparesis
- Other: gastritis, PUD, IBD, GI tract neoplasms

Drugs: morphine, digitalis, cytotoxic agents, bromocriptine

Severe pain: MI, renal colic
Metabolic disorders:
- Uremia, acidosis/alkalosis, hyperglycemia, DKA, thyrotoxicosis

Trauma: blows to the testicles, epigastrium
Vertigo
Reye’s syndrome
↑ ICP

CNS disturbances:
- Trauma, hemorrhage, infarction, neoplasm, infection, hypertensive encephalopathy, migraine

Radiation sickness
N/V of pregnancy, hyperemesis gravidarum

Motion sickness
Bulimia, anorexia nervosa
Psychogenic: emotional disturbances, offensive sights or smells

Severe coughing
Pyelonephritis
CO poisoning

196 WEAKNESS, ACUTE, EMERGENT

Demyelinating disorders (GBS, chronic inflammatory demyelinating polyneuropathy)

Myasthenia gravis
Infectious (poliomyelitis, diphtheria)

Toxic (botulism, tick paralysis, paralytic shellfish toxin, puffer fish, newts)

Metabolic (acquired or familial hypokalemia, hypophosphatemia, hypermagnesemia)

Metals poisoning (arsenic, thallium)

Porphyria
CVA

197 WEIGHT GAIN

Sedentary lifestyle
Fluid overload
Discontinuation of tobacco abuse

Endocrine disorders
- (hypothyroidism, hyperinsulinism associated w/maturity-onset DM, Cushing’s syndrome, hypogonadism, insulinoma, hyperprolactinemia, acromegaly)

Medications (nutritional supplements, oral contraceptives, glucocorticoids, others)

Anxiety disorders w/compulsive eating

Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, other congenital diseases

Hypothalamic injury (rare; <100 cases reported in medical literature)

198 WEIGHT LOSS

Malignant disease
Psychiatric disorders (depression, anorexia nervosa)

New-onset DM
Malabsorption
COPD
AIDS
Uremia, liver disease
Thyrotoxicosis, pheochromocytoma, carcinoid syndrome

Addison’s disease
Intestinal parasites
PUD
IBD
Food faddism
Postgastrectomy syndrome

199 WHEEZING

Asthma
COPD
ILD

Infections (pneumonia, bronchitis, bronchiolitis, epiglottitis)

Cardiac asthma
GERD w/aspiration

Foreign body aspiration
PE
Anaphylaxis

Obstruction airway (neoplasm, goiter, edema or hemorrhage from trauma, aneurysm, congenital abnormalities, strictures, spasm)

Carcinoid syndrome

References
Diseases and Disorders

1 ABSCESS, BRAIN

Diagnosis

H&P
- Classic triad: fever, headache, and focal neurologic deficits depending on location (50% of cases)
- Papilledema (25%)

Labs
- WBC ↑ (60% of pts)
- ESR ↑
- Blood cultures are most often negative (90%).
- LP is contraindicated in pts w/suspected abscess due to elevated ICP (20% die or suffer neurologic decline).
- The yield of Gram stain and culture of material aspirated at time of surgical drainage approaches 100%.

Imaging
- MRI brain with and without gadolinium
- CT w/IV contrast if MRI contraindicated

Etiology
- Contiguous focus of infection (55% of cases): paranasal sinus infection (streptococci, Bacteroides, Haemophilus, Fusobacterium); otitis media/mastoiditis (streptococci, Enterobacteriaceae, Bacteroides, Pseudomonas); dental sepsis (Fusobacterium, Bacteroides, Streptococcus); penetrating head injury (S. aureus, Clostridium); postoperative (S. epidermidis, S. aureus)
- Hematogenous spread (25% of cases): endocarditis (S. aureus, viridans strep); CHD (streptococci, Haemophilus species); UTI (Enterobacteriaceae, Pseudomonadaceae); lung (strep, Actinomyces, Fusobacterium); intra-abd (strep, Enterobacteriaceae, anaerobes)
- Immunocompromised host: Toxoplasma, fungi, Nocardia, Listeria, Enterobacteriaceae
- Cryptogenic (unknown source): 20%

Treatment
- If abscess <2.5 cm and pt is neurologically stable and conscious, start abx and observe.
- Empiric abx Rx: varies w/abscess, location, suspicion of primary source, presence of single or multiple abscesses, pt’s underlying medical condition (e.g., HIV, immunocompromised status)
- Otitis media/mastoiditis: cefotaxime 2 g q4h IV or ceftriaxone 2 g q12h IV plus metronidazole 7.5 mg/kg q6h IV or 15 mg/kg q12h IV
- Dental infection: PCN G 6 million units q6h plus metronidazole 7.5 mg/kg q6h IV
- Head trauma or post cranial surgery: third-generation cep (cefotaxime 2 g IV q6h or ceftriaxone 2 g IV q12h) plus metronidazole 7.5 mg/kg IV q6h or 15 mg/kg IV q12h and nafcillin 2 g IV q4h or vancomycin (30 mg/kg IV in two divided doses adjusted for renal function)
Hematogenous spread (CHD, endocarditis, urinary tract, lung, intra-abd): nafcillin or vancomycin plus metronidazole plus third-generation cep (cefotaxime 2 g IV q6h or ceftriaxone 2 g IV q12h)

Duration of abx Rx: 4-8 wk, w/repeated neuroimaging to ensure adequate treatment (imaging suggested every wk for first 2 wk of Rx, then every 2 wk until abx finished, and then every 2-4 mo for 1 yr to monitor for disease recurrence)

Indications for surgical intervention:
- Collect specimens for C&S
- Reduce mass effect
- Stereotactic bx or aspirate of abscess if surgically feasible
- Timing and choice of surgery depend on:
  - Primary infection source
  - Number and location of the abscesses
  - Whether the procedure is diagnostic or therapeutic
  - Neurologic status of the pt
- Hyperosmolar agents such as mannitol may be indicated if pt is still suffering from sx of ↑ ICP after abx and other Rx.

Clinical Pearl
- Medical Rx is never a substitute for surgical intervention to relieve ↑ ICP.

2 ABSCESS, BREAST

Diagnosis

H&P
- Painful erythematous induration occasionally w/draining through the overlying skin or nipple opening
- I&D and C&S of abscess content
- 10%-30% of breast abscesses are lactational.
- Acute mastitis may develop into a breast abscess if untreated.

Labs
- C&S of aspiration of abscess contents

Imaging
- If mammogram or U/S is required but prevented by discomfort, perform after resolution of abscess.

Etiology
- Lactational abscess: S. aureus
- Subareolar abscess: anaerobes, staphylococci, streptococci

Treatment
- Established abscess: I&D
- Bx of abscess cavity wall to exclude carcinoma
- Abx: nafcillin or oxacillin 2 g q4h IV or cefazolin 1 g q8h IV for 10-14 days; alternative includes vancomycin 1 g IV q12h
- If acute mastitis with abscess (no MRSA): dicloxacillin 500 mg PO q6h or nafcillin/oxacillin 2 g, IV q12h.
- Subareolar abscess: broad-spectrum abx treatment (e.g., cephalixin 500 mg PO qid or cefazolin 1 g q8h IV for 10-14 days for more severe infection) plus metronidazole 500 mg IV/PO tid and drainage are needed to control acute phase.

Clinical Pearls
- Lactational abscess: possible to continue breastfeeding w/o apparent risk of infection to the infant
- Subareolar abscess: notorious for recurrence or complication of fistula formation

3 ABSCESS, EPIDURAL

Definition
Localized collection of pus between the dura mater and the overlying skull (cranial epidural abscess) or vertebral column (spinal epidural abscess).
Diseases and Disorders

Chapter 3

Diagnosis

Clinical Presentation
- Cranial: fever, headache, seizures; onset may be insidious and overshadowed by the primary focus of infection (i.e., sinusitis, otitis media)
- Epidural: fever, backache, nerve root pain, spinal cord dysfunction

Imaging
- MRI w/gadolinium

Etiology
- Spinal epidural abscess: S. aureus (50%-90%), aerobic gram-negative bacilli (12%-17%), aerobic and anaerobic streptococci (8%-17%).
- Spinal epidural abscess is usually due to hematogenous spread. It may also be due to extension from vertebral osteomyelitis.
- Cranial abscesses may be due to spread of initial focus from paranasal sinuses, middle ear, or mastoid cells. It can also be secondary to trauma.

Treatment
- Surgical drainage
- Empiric Rx: Anti-staph (vancomycin) plus aerobic gram-negative bacilli (cefepime, ceftazidime, meropenem)

Clinical Pearl
- Gradenigo’s syndrome (involvement of cranial nerves V and VI w/unilateral facial pain and weakness of the lateral rectus muscle) is due to epidural abscess near the petrous bone.

4 ABSCESS, LIVER

Definition
Necrotic infection of the liver, usually classified as pyogenic or amebic.

Diagnosis

H&P
- RUQ abd pain, fever, nausea, cough w/pleuritic chest pain, anorexia, jaundice

Labs
- Leukocytosis, + blood cultures (50%), ↑ INR (70%), ↑ alkaline phosphatase >90%, ↑ ALT/AST (50%), + stool samples for E. histolytica (10%-15%).
  Serologic testing for E. histolytica does not differentiate acute from prior infection.

Imaging
- CT of abd is imaging study of choice.
- U/S has 80%-95% sensitivity.
- CT- or U/S-guided aspiration (50% sterile) in suspected pyogenic abscess

Etiology
- Pyogenic abscess: usually polymicrobial (streptococcal species [37%], E. coli [33%], K. pneumoniae [18%], Pseudomonas, Proteus, Bacteroides)
- Sources of pyogenic abscess: biliary disease w/cholangitis, gallbladder disease, diverticulitis, appendicitis, penetrating wounds, hematogenous
- Amebic abscess: Entamoeba histolytica. Transmission is usually due to fecal-oral contamination w/invasion of intestinal mucosa and portal system.

Treatment
- Rx of pyogenic liver abscess differs from that of amebic liver abscess.
- Medical management is the cornerstone of Rx in amebic liver abscess, whereas early intervention in the form of surgical Rx or catheter drainage and parenteral abx is the rule in pyogenic liver abscess.
- Percutaneous drainage under CT or U/S guidance is essential in the treatment of pyogenic liver abscesses.
- Aspiration of hepatic amebic abscesses is not useful unless there is no response to treatment or a pyogenic cause is being considered.
- Empiric broad spectrum abx are recommended initially until culture results are available:
  - Metronidazole (500 mg IV q8h) plus a quinolone (ciprofloxacin 400 mg IV q12h or levofloxacin 500 mg IV qd) for amebic abscess
- Monotherapy w/a β-lactam/β-lactamase inhibitor, such as piperacillin-tazobactam (4.5 g q6h), ticarcillin-clavulanate (3.1 g q4h), or ampicillin-sulbactam (3 g q6h)
- Monotherapy w/a carbapenem, such as imipenem (500 mg IV q6h), meropenem (1 g q8h), or ertapenem (1 g qd)
- In pts w/PCN allergy, clindamycin 600-900 mg IV q8h w/an AG
- Duration of abx Rx: 4-6 wk

Abx Rx for amebic liver abscesses:
- Metronidazole 750 mg PO tid for 10 days followed by paromomycin 500 mg tid for 7 days
- Dehydroemetine 1 mg/kg/day IM for 5 days followed by chloroquine 1 g/day for 2 days; then 500 mg/day for 2-3 wk can be used as an alternative to metronidazole

**Clinical Pearl**
- CXR is abnl in 50% of cases: elevated right hemidiaphragm, pleural effusion, subdiaphragmatic air fluid levels.

### 5 ABSCESS, LUNG

#### Diagnosis

**H&P**
- Fever, cough, sputum production (purulent w/foul odor), hemoptysis
- Dullness to percussion, whispered pectoriloquy and bronchophony

**Labs**
- Blood tests are not specific and rarely helpful: CBC w/leukocytosis, blood cultures, sputum Gram stain and culture.
- Fiberoptic bronchoscopy with use of bronchial brushings or BAL fluid is the most widely used intervention in trying to obtain diagnostic bacteriologic cultures.

**Imaging**
- CXR: cavitary lesion w/an air-fluid level
- Chest CT: can localize and size the lesion and assist in differentiating lung abscess from other processes

#### Etiology
- Aspiration is most common factor.
- 90% of abscesses are caused by anaerobic microorganisms (*Bacteroides fragilis, Fusobacterium, Peptostreptococcus*).
- In most cases, anaerobic infection is mixed w/aerobic or facultative anaerobic organisms (*S. aureus, E. coli, K. pneumoniae, P. aeruginosa*).
- Immunocompromised hosts may become infected w/Aspergillus, *Mycobacteria, Nocardia*, and *Rhodococcus equi*.

#### Treatment
- PCN 1-2 million U IV q4h until improvement, followed by PCN V K 500 mg qid for at least 3 wk
- Metronidazole is given w/PCN at doses of 7.5 mg/kg IV q6h followed by PO 500 mg bid-qid.
- Clindamycin is an alternative choice if concerned about PCN resistance. Dose is 600 mg IV q8h followed by 300 mg PO q6h.

#### Clinical Pearls
- Risk factors: alcoholism, seizure disorder, CVA w/dysphagia, poor oral hygiene, bronchiectasis, obstructive lung lesions, esophageal disorders, drug abuse
- Cure rate >95% w/appropriate abx
- Necrotizing pneumonia is similar to lung abscess but differs in size (<2 cm in diameter) and number (usually multiple suppurative cavitary lesions).

### 6 ABSCESS, PELVIC

#### Diagnosis

**H&P**
- Abd or pelvic pain, fever, nausea, abnl bleeding, vaginal d/c
## ABSCESS, PERIRECTAL

### Diagnosis

**H&P**
- Localized perirectal or anal pain, often worsened with movement or straining; perirectal erythema or mass by inspection or palpation

**Labs**
- CBC w/diff; local aerobic and anaerobic cultures; blood cultures if toxic, febrile, or immunocompromised

**Imaging**
- Sigmodioscopy in selected cases
- Imaging studies (pelvic CT) usually not indicated unless extensive disease abscess or immunocompromised pt

### Etiology

- Polymicrobial aerobic (S. aureus, Streptococcus species, E. coli) and anaerobic bacteria (B. fragilis, Peptostreptococcus species, Prevotella species, Fusobacterium species)

### Treatment

- I&D
- Débridement if necrotic tissue
- R/o need for fistulectomy
- Local wound care—packing
- Sitz baths
- Abx Rx: directed toward coverage for mixed skin and enteric flora

**Outpatient**—PO:
- Amoxicillin/clavulanic acid 875-1000 mg bid
- Ciprofloxacin 750 mg PO q12h plus metronidazole 500-750 mg PO q8h or
- Clindamycin 150-300 mg PO q8h

**Inpatient**—IV:
- Amoxicillin-sulbactam (Unasyn) 1.5-3 g IV q6h
- Cefotetan 1-2 g IV q8h
- Piperacillin-tazobactam 3.375 g IV q6-8h
- Imipenem 500-1000 mg IV q8h

### Clinical Pearl

- Many pts will have predisposing underlying conditions (DM, malignant neoplasm or leukemia, immune deficiency, steroid Rx, recent surgery).
8 ABSCESS, PERITONSILLAR

Definition
Peritonsillar abscess is an acute infection located between the capsule of the palatine tonsil and the superior constrictor muscle of the pharynx.

Diagnosis
H&P
- Sore throat, which may be severe; dysphagia and odynophagia; otalgia; foul-smelling breath
- Facial swelling, drooling, headache, fever, trismus
- Hoarseness, muffled voice (also called “hot potato voice”)
- Tender submandibular and anterior cervical lymph nodes, tonsillar hypertrophy, contralateral deflection of the uvula, stridor

Labs
- Rapid strep antigen-detecting testing and throat swab C&S
- Aspiration of the abscess for C&S

Imaging
- CT soft tissue of neck

Etiology
- Peritonsillar abscess is a complication of tonsillitis.
- Group A beta-hemolytic streptococcus is the most common bacterial cause, accounting for 15%-30% of cases in children and 5%-10% of cases in adults.
- Less common aerobic causes are S. aureus, H. influenzae, Neisseria species.
- The most common anaerobic organism is Fusobacterium.

Treatment
- Empiric abx Rx:
  - PO: amoxicillin/clavulanic acid 875 mg bid, PCN VK 500 mg qid plus metronidazole 500 mg qid, or clindamycin 600 mg bid
  - IV: ampicillin-sulbactam 3 g q6h or clindamycin 900 mg q8h
- Steroids may be helpful in reducing sx and speeding recovery.
- Tonsillectomy: 3-6 mo after dx
- Although rare, in adults and children w/peritonsillar abscess and a h/o recurrent pharyngitis or previous peritonsillar abscess, the specialist may proceed w/removal of the tonsils directly after prescribing the pt IV abx. This is known as a quinsy or hot tonsillectomy.

Clinical Pearl
- Complications of peritonsillar abscess include airway obstruction, lung abscess or aspiration pneumonitis, GN, rheumatic fever, erosion into carotid sheath, and extension of infection into the tissues of the deep neck or posterior mediastinum.

9 ABSCESS, RETROPHARYNGEAL

Definition
Retropharyngeal abscess is a soft tissue infection of the throat involving the retropharyngeal space. The anatomic boundaries of the retropharyngeal space are the middle layer of the deep cervical fascia (abutting the posterior esophageal wall) anteriorly and the deep layer of the deep cervical fascia posteriorly. These two fasciae fuse inferiorly at the level between the first and second thoracic vertebra.

Diagnosis
H&P
- The onset may be insidious, w/little more than fever, irritability, drooling, a muffled voice (dysphonia), or possibly nuchal rigidity.
- The pt may have intense dysphagia, drooling, and odynophagia, or there may be some element of respiratory distress from edema and inflammation of the airway (stridor, tachypnea, or both).
- Unwillingness to move the neck because of discomfort is often a prominent presenting feature and should lead to consideration of retropharyngeal abscess if a child is febrile and irritable.
Diseases and Disorders

Chapter 3

- Extension of the neck is usually affected more than flexion. This causes the pt to hold his or her neck stiffly or to present w/torticollis.
- Trismus is unusual.
- PE: may be possible to appreciate midline or unilateral swelling of the posterior pharyngeal wall. The mass may be fluctuant to the examining finger, and care must be taken to avoid rupture of the abscess into the upper airway.

Imaging
- CT of soft tissues of the neck
- MRI of neck w/gadolinium is more sensitive than CT.

Etiology
- The predominant bacterial species are S. pyogenes (group A streptococcus), S. aureus, and respiratory anaerobes (including Fusobacterium, Prevotella, and Veillonella species). Haemophilus species are also occasionally found.
- In young children, infection usually reaches this space by lymphatic spread from a septic focus in the pharynx or sinuses.
- In adults, infection may reach the retropharyngeal space from either local or distant sites. Penetrating trauma (e.g., from chicken bones or after instrumentation) is the usual source of local spread. More distant sources of infection include odontogenic sepsis and peritonsillar abscess (now a rare cause).

Treatment
- High-dose PCN (2-4 million units IV q4h) plus metronidazole (1 gm IV loading dose then 500 mg IV q6h) or ampicillin-sulbactam (50 mg/kg/dose IV q6h) or clindamycin (600-900 mg IV q8h)
- Surgical: drainage is indicated when there is a large hypodense area or when a pt has failed to respond to parenteral Rx alone.

Clinical Pearl
- Complications are numerous and could be fatal; these include airway obstruction, septicemia, thrombosis of the internal jugular vein, carotid artery rupture, and acute necrotizing mediastinitis. Aspiration w/resultant pneumonia may complicate retropharyngeal abscess if rupture of the abscess occurs and empties into the airway. The most dreaded complication is jugular vein supplicative thrombophlebitis (Lemierre’s syndrome), in which the vessels of the carotid sheath become infected, leading to bacteremia and metastatic spread of infection to the lungs, brain, and mediastinum.

10) ABSCESS, SPINAL EPIDURAL

Diagnosis
H&P
- Fever, malaise, and back pain are the most consistent early sx; pain is often focal.
- As the disease progresses, root pain can occur, followed by motor weakness, sensory changes, bladder and bowel dysfunction, and paralysis.
- Damage to the spinal cord can be caused by direct compression of the spinal cord, vascular compromise, bacterial toxins, and inflammation.

Labs
- WBC ↑ or nl
- ESR ↑
- Blood cultures (+ 60% pts)
- CSF cultures (+19%), but LP unnecessary and may be contraindicated
- CT-guided aspiration or open bx should be done to determine causative organism; abscess content culture + in 90%.

Imaging
- MRI w/gadolinium; CT scan w/contrast may show the abscess but is less sensitive than MRI.
- CT myelogram for suspected cord compression
Etiology
- Pyogenic bacteria account for the majority of cases in the U.S. The most common causative organism is S. aureus. Immigrants from TB-endemic areas may present w/TB SEAs. Fungi and parasites can also cause this condition. Most posterior SEAs are thought to originate from distant focus (e.g., skin and soft tissue infections); anterior SEAs are commonly associated w/diskitis or vertebral osteomyelitis. No source found in approximately one third of cases.
- Associated predisposing conditions include DM, alcoholism, cancer, AIDS, and chronic renal failure, or after epidural anesthesia, spinal surgery or trauma, or IV drug use. No predisposing condition in 20% of pts.

Treatment
- Surgical decompression
- Abx directed at the most likely organism. If MRSA is possible: vancomycin 1 g IV q12h. If MRSA is unlikely: nafcillin or oxacillin 2 g IV q4h.
- If the organism is unknown, broad coverage against staphylococci, streptococci, and gram-negative bacilli should be initiated. The regimen can be adjusted according to culture results. Rx should continue for at least 4–6 wk.

11 ACETAMINOPHEN POISONING

Diagnosis
H&P
- Clinical presentation variable on dose ingested and time from ingestion. Initially malaise, N/V, diaphoresis, followed by somnolence, coma, and jaundice. After the initial 12–24 hr, pts may also complain of RUQ pain.

Labs
- STAT plasma acetaminophen level, w/a second level drawn approximately 4–6 hr after the initial level. Subsequent levels can be obtained q2–4h until the levels stabilize or decline. These levels can be plotted using the Rumack-Matthew nomogram (Fig. 3-1) to calculate potential hepatic toxicity. The nomogram cannot be used when pts present >24 hr after ingestion, for those who ingested an extended-release preparation, in pts who had a repeated supratherapeutic ingestion, or when the time of ingestion is unknown.
- Hepatotoxicity is defined as any ↑ in AST; severe hepatotoxicity is AST >1000 IU/L; hepatic failure is hepatotoxicity w/hepatic encephalopathy. For those who cannot be risk stratified by the nomogram, the American College of Emergency Physicians recommends that N-acetylcysteine be administered to those older than 12 yr w/hepatic failure thought to be caused by acetaminophen. It should also be administered to pts >12 yr of age who have hepatotoxicity thought to be caused by acetaminophen and a suspected or known acetaminophen OD.
- AST, ALT, bilirubin, PT, BUN, and Cr should be initially obtained on all pts.
- Serum and urine toxicology screen for other potential toxic substances and screening for infectious hepatitis are also recommended on admission.

Treatment
- Gastric lavage and administer activated charcoal if the pt is seen within 1 hr of ingestion or the clinician suspects polydrug ingestion.
- If acetaminophen level is in the toxic range, start N-acetylcysteine either IV or PO. Acetylcysteine IV loading dose is 150 mg/kg during 15–60 min × 1. Maintenance dose is 50 mg/kg during 4 hr, followed by 100 mg/kg during 16 hr. The dose does not require adjustment for renal or hepatic impairment or for dialysis. PO administration consists of 140 mg/kg as a loading dose, followed by 70 mg/kg q4h for a total of 17 doses. N-acetylcysteine Rx should be started within 24 hr of acetaminophen OD. If charcoal Rx was initially instituted, lavage the stomach and recover as much charcoal as possible; then instill N-acetylcysteine, ↑ the loading dose by 40%. Advantages of IV administration include more reliable absorption, fewer doses, and shorter duration of treatment (1 day vs. 3 days).
- Monitor acetaminophen level; use graph to plot possible hepatic toxicity. Repeat ALT and acetaminophen levels after 12–14 hr of IV acetylcysteine.
ACETAMINOPHEN POISONING

Probable hepatic toxicity
Possible hepatic toxicity
Hepatic toxicity unlikely

**Figure 3-1.** Rumack-Matthew nomogram for acetaminophen poisoning.

- Infusion. Continuing infusion >16 hr if AST levels are ↑ or if the serum acetaminophen concentration is measurable.
- Provide adequate IV hydration (e.g., D$_5$W/NS at 150 mL/hr).
- In pt receiving IV N-acetylcysteine and with liver failure, frequent monitoring of VS, oxygen saturation by pulse oximetry, AST, serum Cr, and for signs of hypoglycemia and infection is essential.
- If acetaminophen level is nontoxic, N-acetylcysteine Rx may be discontinued after 24 hr. If evidence of liver injury, continue for 72 hr.

**Clinical Pearl**
- The amount of acetaminophen necessary for hepatic toxicity varies w/the pt’s body size and hepatic function. A toxic dose of acetaminophen usually exceeds 7.5 g or 140 mg/kg in adults.
1. Evaluate serum electrolytes and ABGs. Draw ABG and electrolyte samples concomitantly and check:
   - Plasma HCO₃⁻:
     • ↑ in metabolic alkalosis or respiratory acidosis (compensated)
     • ↓ in metabolic acidosis or respiratory alkalosis (compensated)
   - Serum K⁺ (ΔpH 0.1 = ΔK⁺ 0.6):
     • ↑ in acidemia
     • ↓ in alkalemia
   - Serum Cl⁻: compare w/plasma Na⁺ concentration; they should be proportionately ↑ or ↓ if the change in Cl⁻ concentration is the result of a change in the hydration of the pt.
     • If the Cl⁻ is disproportionately ↑: metabolic acidosis or respiratory alkalosis.
     • If the Cl⁻ is disproportionately ↓: metabolic alkalosis or respiratory acidosis.

2. Evaluate type of disturbance present by examining pH, $P_{CO_2}$, and $HCO_3^−$. See Figure 3-2.

3. Calculate degree of compensation:
   - **Simple acid-base disorders** (metabolic acidosis, metabolic alkalosis, respiratory acidosis, respiratory alkalosis) $\rightarrow$ adequate compensation
   - **Mixed acid-base disorders** $\rightarrow$ simultaneous presence of two or more abnormalities (Box 3-1)
   - **Metabolic acidosis**:
     - $↓$ from nl $P_{CO_2} = 1.3 \times ↓$ from nl $HCO_3^−$; ($P_{CO_2} =$ last two digits of the pH)
     - If actual $P_{CO_2}$ is $>calculated$ $→$ both metabolic and respiratory acidosis are present.
     - If actual $P_{CO_2}$ is $<calculated$ $→$ both metabolic acidosis and respiratory alkalosis are present.
   - **Respiratory acidosis**:
     - Acute: $↑$ $P_{CO_2}$ by 10 = $↓$ pH by 0.08 and $↑$ $HCO_3^−$ by 1 mEq/L (usual upper limit of compensation is $HCO_3^− = 30$ mEq/L)
     - Chronic: $↑$ $P_{CO_2}$ by 10 = $↓$ pH by 0.03 and $↑$ $HCO_3^−$ by 3.5 mEq/L (usual upper limit of compensation is $HCO_3^− = 55$ mEq/L)
   - **Metabolic alkalosis**:
     - $↑$ $HCO_3^−$ by 1 = $↑$ pH by 0.015 and $↑$ $P_{CO_2}$ by 0.7
     - Limitations: the compensatory response ($↑$ $P_{CO_2}$) is limited to a max $P_{CO_2}$ of 55.
     - There is an impaired compensatory response in pts w/COPD, heart failure, and hepatic coma.

---

**Box 3-1: Common Causes of Mixed Disturbances Associated with Metabolic Acidosis**

**Mixed Anion Gap Acidosis**
- Ketoacidosis and lactic acidosis
- Methanol or ethylene glycol intoxication and lactic acidosis
- Uremic acidosis and ketoacidosis

**Mixed Anion Gap and Hyperchloremic Acidosis**
- Diarrhea and lactic acidosis or ketoacidosis
- Progressive renal failure
- Type IV renal tubular acidosis and DKA
- DKA during treatment

**Mixed Hyperchloremic Acidosis**
- Diarrhea and renal tubular acidosis
- Diarrhea and hyperalimentation
- Diarrhea and acetazolamide or mafenide

**Anion Gap Acidosis or Hyperchloremic Acidosis and Metabolic Alkalosis**
- Ketoacidosis and protracted vomiting or NG suction
- Chronic renal failure and vomiting or NG suction
- Diarrhea and vomiting or NG suction
- Renal tubular acidosis and vomiting
- Lactic acidosis or ketoacidosis plus NaHCO₃ Rx

**Anion Gap Acidosis or Hyperchloremic Acidosis and Respiratory Alkalosis**
- Respiratory alkalosis
- Lactic acidosis
- Salicylate poisoning
- Hepatic disease
- Gram-negative sepsis
- Pulmonary edema

**Anion Gap Acidosis or Hyperchloremic Acidosis and Respiratory Acidosis**
- Cardiopulmonary arrest
- Pulmonary edema
- Respiratory failure in chronic lung disease
- Phosphate depletion
- Drug OD and poisoning
Respiratory alkalosis:
- Acute: ↓ Paco₂ by 10 = ↑ pH by 0.08 and ↓ HCO₃⁻ by 2.5
- Chronic: ↓ Paco₂ by 10 = ↑ pH by 0.03 and ↓ HCO₃⁻ by 5

4. Determination of AG: AG = Na⁺ – (Cl⁻ + HCO₃⁻)

- NI AG = 9-14 mEq/L.
- Most common cause of ↑ AG is metabolic acidosis, in which HCO₃⁻ is titrated by organic acids such as lactic acid and keto acids.
- Compare the ∆AG w/the ∆HCO₃⁻. For each ↑ of 1 mEq in AG, there should be ↓ in serum HCO₃⁻. Discrepancies in these changes may indicate mixed acid-base disturbances.
- When the AG is ≥25-30 mEq/L, an organic acidosis is almost always present, regardless of whether the HCO₃⁻ level is reduced.
- Other factors may affect what a “nl” AG will be in a given pt—most commonly hypalbuminemia ↓ the AG by ↓ unmeasured anions. Hyperkalemia also does this by ↑ unmeasured cations.

ACIDOSIS, METABOLIC

Diagnosis (Fig. 3-3)
- Evaluate serum electrolytes and ABGs. Draw ABG and electrolyte samples concomitantly:
  - Plasma HCO₃⁻
    - ↑ in metabolic alkalosis or respiratory acidosis (compensated)
    - ↓ in metabolic acidosis or respiratory alkalosis (compensated)
  - Serum K⁺ (ΔpH 0.1 = ΔK⁺ 0.6)
    - ↑ in acidemia
    - ↓ in alkalemia

- If actual Paco₂ is > calculated, then both metabolic and respiratory acidosis are present
- If actual Paco₂ is < calculated, then both metabolic acidosis and respiratory alkalosis are present

Hyperchloremic acidosis (e.g., RTA, intestinal loss of HCO₃⁻ [diarrhea, pancreatic fistula], drugs [acetazolamide, amiloride, triamterene])

AG acidosis (e.g., lactic acidosis, ketoacidosis, uremia, ingestion of toxins [methanol, ethylene glycol, salicylates])

FIGURE 3-3. Diagnostic algorithm for metabolic acidosis.
• Serum Cl⁻: compare w/plasma Na⁺ concentration; they should be proportionately ↑ or ↓ if the ΔCl⁻ concentration is the result of a Δ in the hydration of the pt.
  • If the Cl⁻ is disproportionately ↑, think of metabolic acidosis or respiratory alkalosis.
  • If the Cl⁻ is disproportionately ↓, think of metabolic alkalosis or respiratory acidosis.

Evaluate type of disturbance present by examining pH, PCO₂, and HCO₃⁻.
Calculate the degree of compensation to distinguish the following:
  • Simple acid-base disorders (metabolic acidosis, metabolic alkalosis, respiratory acidosis, respiratory alkalosis): adequate compensation
  • Mixed acid-base disorders: simultaneous presence of two or more abnormalities

The following formulas are used to calculate if the degree of compensation is adequate:
  • If adequate compensation, in metabolic acidosis, ↓ from nl PaCO₂ should equal 1.3 × ↓ from nl HCO₃⁻; usually PaCO₂ = last 2 digits of the pH.
  • If actual PaCO₂ is > calculated, both metabolic and respiratory acidosis are present.
  • If actual PaCO₂ is < calculated, both metabolic acidosis and respiratory alkalosis are present.

Etiology
  • Metabolic acidosis w/↑ AG (AG acidosis)
    • Lactic acidosis
    • Ketoacidosis (DM, alcoholic ketoacidosis)
    • Uremia (chronic renal failure)
    • Ingestion of toxins (paraldehyde, methanol, salicylate, ethylene glycol)
    • High-fat diet (mild acidosis)
  • Metabolic acidosis w/nl AG (hyperchloremic acidosis)
    • Renal tubular acidosis (including acidosis of aldosterone deficiency)
    • Intestinal loss of HCO₃⁻ (diarrhea, pancreatic fistula)
    • Carbonic anhydrase inhibitors (e.g., acetazolamide)
    • Dilutional acidosis (as a result of rapid infusion of bicarbonate-free isotonic saline)
    • Ingestion of exogenous acids (ammonium chloride, methionine, cystine, Ca chloride)
    • Ileostomy
    • Ureterosigmoidostomy
    • Drugs: amiloride, triamterene, spironolactone, β-blockers

Treatment
  • Correct underlying cause (e.g., DKA, diarrhea, uremia)

Clinical Pearls
  • Measurement of urinary AG (U₉⁺ + U₉⁻ − U₉Cl⁻) and urinary pH is useful in the diff dx of hyperchloremic metabolic acidosis:
    • Negative urinary AG suggests GI loss of HCO₃⁻.
    • Positive urinary AG suggests altered distal urinary acidification.
    • Low urinary pH and ↑ plasma K⁺ in pts w/positive urinary AG suggest selective aldosterone deficiency.
    • Urinary pH >5.5 and ↑ plasma K⁺ suggest hyperkalemic distal renal tubular acidosis.
    • Urinary pH >5.5 and nl/↓ plasma K⁺ indicate classic renal tubular acidosis.
  • The mnemonic MUDPILES is useful to remember the causes of AG acidosis:
    • Methanol
    • Uremia
    • DKA, alcoholic ketoacidosis (AKA), starvation ketoacidosis (SKA)
    • Paraldehyde, phenformin (or metformin)
    • Iron, isoniazid
    • Lactic acidosis (cyanide, H₂S, CO, MetHb)
    • Ethylene glycol
    • Salicylates
ACIDOSIS, RESPIRATORY

Diagnosis
- Evaluate serum electrolytes and ABGs. Draw ABG and electrolyte samples concomitantly:
  - Plasma HCO$_3^-$
    - ↑ in metabolic alkalosis or respiratory acidosis (compensated)
    - ↓ in metabolic acidosis or respiratory alkalosis (compensated)
  - Serum K$^+$ (ΔpH 0.1 = ΔK$^+$ 0.6)
    - ↑ in acidemia
    - ↓ in alkalemia
  - Serum Cl$^-$: compare w/plasma Na$^+$ concentration; they should be proportionately ↑ or ↓ if the Δ in Cl$^-$ concentration is the result of a Δ in the hydration of the pt.
    - If the Cl$^-$ is disproportionately ↑, think of metabolic acidosis or respiratory alkalosis.
    - If the Cl$^-$ is disproportionately ↓, think of metabolic alkalosis or respiratory acidosis.
- Evaluate type of disturbance present by examining pH, PCO$_2$, and HCO$_3^-$. Calculate the degree of compensation:
  - Simple acid-base disorders (metabolic acidosis, metabolic alkalosis, respiratory acidosis, respiratory alkalosis) = adequate compensation.
  - Mixed acid-base disorders = simultaneous presence of two or more abnormalities.
  - The following formulas are used to calculate whether the degree of compensation is adequate (Fig. 3-4):
    - Acute: ↑ PaCO$_2$ by 10 = ↓ pH by 0.08 and ↑ HCO$_3^-$ by 1 mEq/L (usual upper limit of compensation is HCO$_3^-$ = 30 mEq/L).
    - Chronic: ↑ PaCO$_2$ by 10 = ↓ pH by 0.03 and will ↑ HCO$_3^-$ by 3.5 mEq; (usual upper limit of compensation is HCO$_3^-$ = 55 mEq/L).
- Confirm type of disturbance present by examining pH, PCO$_2$, and HCO$_3^-$. (see Fig. 3-3).

![Diagnostic algorithm for respiratory acidosis.](image)

Etiology
- Pulmonary disease (COPD, severe pneumonia, pulmonary edema, interstitial fibrosis)
- Airway obstruction (foreign body, severe bronchospasm, laryngospasm)
- Thoracic cage disorders (pneumothorax, flail chest, kyphoscoliosis)
- Defects in muscles of respiration (myasthenia gravis, hypokalemia, muscular dystrophy)
- Defects in PNS (amyotrophic lateral sclerosis, poliomyelitis, GBS, botulism, tetanus, organophosphate poisoning, spinal cord injury)
- Depression of respiratory center (anesthesia, narcotics, sedatives, vertebral artery embolism or thrombosis, ↑ ICP)
- Failure of mechanical ventilator
ACRONEGALY

Definition
Chronic disorder resulting from the effects of either hypersecretion of GH or ↑ amounts of IGF-1.

Diagnosis
H&P
- Prognathism; h/o ↑ hat, glove, and shoe size; coarse features resulting from growth of soft tissue; headache, arthralgias, muscle weakness, HTN, visual field deficits, carpal tunnel syndrome

Labs
- ↑ Serum IGF-1 is best initial screening test.
- Failure to suppress serum GH to <2 ng/mL after 100 g oral glucose is considered diagnostic.
- GHRH level >300 ng/mL is indicative of an ectopic source of GH.
- Baseline labs may reveal ↑ serum phosphate and ↑ urine Ca.

Imaging
- MRI of pituitary and hypothalamus is best diagnostic imaging study.

Etiology
- Pituitary adenoma affecting anterior lobe
- Ectopic production of GH-releasing hormone from a carcinoid or other neuroendocrine tumor

Treatment
- Transsphenoidal microsurgical adenomectomy is Rx of choice.
- Irradiation can be used to reduce further tumor growth.
- Medical Rx is indicated when surgery has failed, or surgery is contraindicated, or while waiting for effects of radiotherapy to begin.
- Medical Rx consists of octreotide (somatostatin analogue), bromocriptine (dopamine analogue), or pegvisomant (GH-receptor antagonist).

ACTINOMYCOSIS

Definition
Infection caused by both anaerobic or microaerophilic bacteria that normally colonize the mouth, vagina, and colon. It is characterized by the formation of painful abscesses, soft tissue infiltration, and draining sinuses.

Diagnosis
H&P
- Cervicofacial disease presents w/painful soft tissue swelling at the angle of the mandible and generally occurs in the setting of poor dental hygiene, recent dental surgery, or minor oral trauma.
- Thoracic disease can involve the lungs, pleura, mediastinum, or chest wall secondary to aspiration of Actinomyces organisms in pts w/poor oral hygiene.
- Abd disease frequently affects the ileocecal valve and occurs most commonly after appendectomy, perforated bowel, diverticulitis, or surgery to the GI tract.

Labs
- Dx requires obtaining specimens either by aspirating abscesses, excising sinus tracks, or tissue biopsies.
- Isolating nests of Actinomyces species (sulfur granules) from tissue specimens or draining sinuses confirms the dx.

Imaging
- CT of head, chest, abd, and pelvic areas is useful in localizing site and spread of infection.

Etiology
- Most commonly Actinomyces israelii
Diseases

- Acute coronary syndrome (ACS) includes unstable angina/non–ST-segment elevation myocardial infarction (STEMI) and ST-segment elevation myocardial infarction (STEMI).

- Clinical pearls:
  - Actinomycosis infections are polymicrobial, usually associated w/S. aureus, Bacteroides, Eikenella corrodens, Enterococcus, and Fusobacterium.
  - There is no person-to-person transmission of Actinomyces.

17 ACUTE CORONARY SYNDROME (ACS; MI, STEMI, NSTEMI, UNSTABLE ANGINA)

Definition

ACS are manifestations of ischemic heart disease and represent a broad clinical spectrum that includes non–ST-segment elevation ACS (collectively unstable angina/non–ST elevation MI [NSTEMI]) and ST elevation MI (STEMI). STEMI is defined as ST-segment elevation >0.1 mV in ≥2 contiguous precordial or adjacent limb leads, a new LBBB, or a true posterior MI.

- MI: According to the European Society of Cardiology/ACC, either one of the following criteria for acute evolving or recent MI satisfies the dx:
  - Typical ↑ and gradual fall (troponin) or more rapid ↑ and fall (CK-MB) of biochemical markers of myocardial necrosis w/ at least one of the following:
    - Ischemic sx
    - Development of pathologic Q waves on ECG
    - ECG changes indicative of ischemia (ST-segment elevation or depression)
    - Coronary artery intervention (e.g., coronary angioplasty)
  - Pathologic findings of acute MI: ST elevation MI (area of ischemic necrosis that penetrates the entire thickness of the ventricular wall and results in ST-segment elevation)

- Unstable angina: coronary arterial plaque rupture w/fragmentation and distal arterial embolization resulting in myocardial necrosis; usually occurs w/o ST elevation and is thus termed non–ST elevation MI (NSTEMI).

The European Heart Journal and the Journal of the American College of Cardiology definition of acute MI includes the following subtypes:

- Type 1: spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion or rupture, fissuring, or dissection
- Type 2: MI secondary to ischemia due to either ↑ oxygen demand or ↓ supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, HTN, or hypotension
- Type 3: sudden unexpected cardiac death, including cardiac arrest, often w/sx suggestive of myocardial ischemia, accompanied by presumably new ST elevation, new LBBB, or evidence of fresh thrombus in a coronary artery by angiography or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood
  - Type 4a: MI associated w/percutaneous coronary intervention
  - Type 4b: MI associated w/stent thrombosis as documented by angiography or at autopsy
  - Type 5: MI associated w/CABG

Diagnosis

- H&P:
  - Crushing substernal chest pain usually lasts >20 min.
  - Pain is unrelieved by rest or sublingual NTG or is rapidly recurring.
  - Pain radiates to the left or right arm, neck, jaw, back, shoulders, or abd and is not pleuritic in character.
  - Pain may be associated w/dyspnea, diaphoresis, N/V.
There is no pain in 20% of infarctions (usually in diabetic or elderly pts).
- Skin may be diaphoretic, w/pallor (because of ↓ oxygen).
- Rales may be present at the bases of lungs (indicative of CHF).
- Cardiac auscultation may reveal an apical systolic murmur caused by MR secondary to papillary muscle dysfunction; S₃ or S₄ may also be present.

**Labs** (Fig. 3-5)
- Cardiac troponin levels: cTnT and cTnl ↑ after muscle damage (3-12 hr), peak within 24 hr, and may be present up to 7 days for cTnl and up to 10-14 days for cTnT. cTnT can be falsely + in pts w/renal failure.
- ↑ CK-MB isoenzyme

**Risk Assessment**: Table 3-1

**Imaging**
- CXR
- ECG (Fig. 3-6, Table 3-2)
  - STEMI
    - Inverted T waves (area of ischemia)
    - Elevated ST segment (area of injury): leads V₁-V₆ → anterior or anterolateral MI; leads I and aVL → lateral MI; leads II, III, or aVF → inferior wall MI
    - Q waves (area of infarction, usually develop during 12-36 hr)
  - NSTEMI
    - Hx and enzyme elevations are compatible w/MI
    - ECG shows no ST-segment elevation and sometimes shows a small depression of the ST segment

**Etiology**
- Coronary atherosclerosis
- Coronary artery spasm
- Coronary embolism (caused by infective endocarditis, rheumatic heart disease, intracavitary thrombus)
- Periarteritis and other coronary artery inflammatory diseases
- Dissection into coronary arteries (aneurysmal or iatrogenic)
- Congenital abnormalities of coronary circulation
- MI w/nl coronaries (*MINC syndrome*): more frequent in younger pts and cocaine addicts. The risk of acute MI is ↑ by a factor of 24 during the
### TABLE 3-1  TIMI Risk Score for Patients with Unstable Angina and Non-ST-Segment Elevation MI: Predictor Variables

<table>
<thead>
<tr>
<th>Predictor Variable</th>
<th>Point Value of Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≥3 risk factors for CAD</td>
<td>1</td>
<td>Risk factors: Family history of CAD, Hypertension, Hypercholesterolemia, Diabetes, Current smoker</td>
</tr>
<tr>
<td>Aspirin use in last 7 days</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Recent, severe symptoms of angina</td>
<td>1</td>
<td>≥2 anginal events in the last 24 hours</td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>1</td>
<td>CK-MB or cardiac-specific troponin level</td>
</tr>
<tr>
<td>ST deviation ≥0.5 mm</td>
<td>1</td>
<td>ST depression ≥0.5 mm is significant; transient ST elevation &gt;0.5 mm for &lt;20 minutes is treated as ST-segment depression and is high risk; ST elevation ≥1 mm for more than 20 minutes places these patients in the STEMI treatment category</td>
</tr>
<tr>
<td>Prior coronary artery stenosis ≥50%</td>
<td>1</td>
<td>Risk predictor remains valid even if this information is unknown</td>
</tr>
</tbody>
</table>

Calculated TIMI Risk Score | Risk of ≥1 Primary Endpoint* in ≤14 days | Risk Status |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 or 1</td>
<td>5%</td>
<td>Low</td>
</tr>
<tr>
<td>2</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>13%</td>
<td>Intermediate</td>
</tr>
<tr>
<td>4</td>
<td>20%</td>
<td>High</td>
</tr>
<tr>
<td>5</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>6 or 7</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

*Primary endpoints: new or recurrent MI or need for urgent revascularization.

### TABLE 3-2  ST-Segment Elevation or New or Presumably New LBBB: Evaluation for Reperfusion

**Step 1: Assess time and risk**
- Time since onset of sx
- Risk of STEMI
- Risk of fibrinolysis
- Time required to transport to skilled PC catheterization suite

**Step 2: Select reperfusion (fibrinolysis or invasive) strategy**
- Note: If presentation <3 hr and no delay for PCI, then no preference for either strategy.

<table>
<thead>
<tr>
<th>Fibrinolysis is generally preferred if:</th>
<th>An invasive strategy is generally preferred if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early presentation (≤3 hr from sx onset)</td>
<td>Late presentation (sx onset &gt;3 hr ago)</td>
</tr>
<tr>
<td>Invasive strategy is not an option (e.g., lack of access to skilled PCI facility or difficult vascular access) or would be delayed</td>
<td>Skilled PCI facility available w/surgical backup</td>
</tr>
<tr>
<td>Medical contact-to-balloon or door-balloon &gt;90 min</td>
<td>Medical contact-to-balloon or door-balloon &lt;90 min</td>
</tr>
<tr>
<td>(Door-to-balloon) minus (door-to-needle) is &gt;1 hr</td>
<td>(Door-to-balloon) minus (door-to-needle) is &lt;1 hr</td>
</tr>
<tr>
<td>No contraindications to fibrinolysis</td>
<td>Contraindications to fibrinolysis, including ↑ risk of bleeding and ICH</td>
</tr>
<tr>
<td>Dx of STEMI is in doubt</td>
<td>High risk from STEMI (CHF, Killip class is ≥3)</td>
</tr>
</tbody>
</table>
60 min after the use of cocaine in persons who are otherwise at relatively low risk. Most pts w/cocaine-related MI are young, nonwhite, male cigarette smokers w/o other risk factors for arteriosclerotic heart disease who have a h/o repeated cocaine use. Blood and urine toxicology screen for cocaine is recommended in all young pts who present w/acute MI.

- Hypercoagulable states, ↑ blood viscosity (P. vera)

**Treatment** (Tables 3-3 and 3-4)
- Pts w/STEMI who present ≤12 hr of sx onset and have no contraindications should receive immediate reperfusion Rx (fibrinolysis or PCI). Primary PCI is preferred to fibrinolysis only in high PCI–volume hospitals.
- Rescue PCI: reasonable in those w/≤50% resolution of ST-segment elevation 90 min after initiation of fibrinolytic Rx and moderately large area of myocardium at risk
<table>
<thead>
<tr>
<th>TABLE 3-3</th>
<th>Hemodynamic Categories in Acute MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>CI (L/min/m²)</td>
</tr>
<tr>
<td>NI in acute MI</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>&lt;2.5</td>
</tr>
<tr>
<td>Volume overload</td>
<td>&gt;2.5</td>
</tr>
<tr>
<td>LV failure</td>
<td>&lt;2.5</td>
</tr>
<tr>
<td>Severe LV failure</td>
<td>&lt;2.5</td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 3-4</th>
<th>Electrocardiographic Location of ST Elevation MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area of Infarction</td>
<td>ECG Abnormality</td>
</tr>
<tr>
<td>Anterior wall</td>
<td>Q waves in V₁-V₄</td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>Q waves in V₁-V₂</td>
</tr>
<tr>
<td>Anteropical</td>
<td>Q waves in V₂-V₅</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>Q waves in V₅-V₁₀, I, aVL</td>
</tr>
<tr>
<td>Lateral wall</td>
<td>Q waves in I, aVL</td>
</tr>
<tr>
<td>Inferior wall</td>
<td>Q waves in II, III, aVF</td>
</tr>
<tr>
<td>Posterior wall</td>
<td>R &gt; S in V₁</td>
</tr>
<tr>
<td></td>
<td>Q wave in V₆</td>
</tr>
</tbody>
</table>

CFX, left circumflex artery; LAD, left anterior descending; PDA, posterior descending artery; RCA, right coronary artery.

- Antiplatelet Rx: ASA, 160-325 mg PO unless true ASA allergy is suspected. If the first dose is chewed, a blood level is achieved more rapidly than if it is swallowed. Clopidogrel should be added to ASA Rx in pts w/STEMI, whether or not they undergo reperfusion Rx. PO loading dose is 300 mg, maintenance dose 75 mg. Clopidogrel is indicated in all pts undergoing PCI or stenting. Duration of Rx is variable (drug-eluting stent = 1 yr; bare metal stent ≥1 mo, preferably 1 yr; no stent = 14 days).

- Nitrates: they ↑ the supply of oxygen by reducing coronary vasospasm and ↓ consumption of oxygen by reducing ventricular preload. Sublingual NTG (0.4 mg) can be administered immediately on suspicion of MI (unless systolic BP is <90 mm Hg or ↓ 30 mm Hg below baseline or HR is <50 bpm or >100 bpm); IV NTG can be subsequently used. NTG should be used w/great caution in pts w/inferior wall MI; nitrate usage can result in hypotension because these pts are sensitive to change in preload. It
should also be avoided in pts suspected of having right ventricular infarction (↑ risk of preload reduction) and if a pt has used sildenafil (Viagra) or vardenafil (Levitra) within the previous 24 hr or tadalaﬁl (Cialis) in the previous 48 hr.

- Adequate analgesia: morphine sulfate 2-4 mg IV initially w/increments of 2-8 mg IV at 5- to 15-min intervals can be given for severe pain unrelieved by NTG. Hypotension secondary to morphine can be treated w/careful IV hydration w/saline solution. If sinus bradycardia accompanies hypotension, use atropine (0.5-1.0 mg IV q5min PRN to a total dose of 2.5 mg). Respiratory depression caused by morphine can be reversed w/naloxone 0.8 mg.
- Nasal oxygen: administer at 2-4 L/min.
- β-Blockers: IV β-blockers should be used with caution in pts w/STEMI (↑ risk of cardiogenic shock). They may be considered for Rx of HTN if there are no contraindications. Oral β-blocker Rx should be started within 24 hr in hemodynamically stable pts w/o contraindications.

**Reference**

**Secondary Prevention Post STEMI**
- Smoking cessation
- BP control (<140/90 mm Hg, <130/80 mm Hg in diabetics or renal disease)
- Lipid management (LDL <70 mg/dL)
- Exercise (30 min at least 5 days/wk); weight loss if overweight (keep BMI 18.5-24.9); waist circumference <40 inches in men, <35 inches in women
- Antiplatelet Rx: ASA 75-162 mg (325 mg if stent placed), clopidogrel 75 mg qd (if stent placed)
- β-Blockers (unless contraindicated)
- ACEIs reduce left ventricular dysfunction and dilation and slow the progression of CHF. Commonly used ACEIs are ramipril 2.5 mg qd, captopril 12.5 mg PO bid, enalapril 2.5 mg bid, or lisinopril 2.5-5 mg qd initially, w/subsequent titration as needed. Ramipril is associated w/lower mortality than most ACEIs. Use ARBs in pts intolerant to ACEIs.

18 **ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)**

**Definition**
Form of noncardiogenic pulmonary edema that results from acute damage to the alveoli. The definition of ARDS includes the following components: a ratio of PaO2 to the FiO2 ≤200, regardless of the level of PEEP; the detection of bilateral pulmonary infiltrates on the frontal CXR; PAWP ≤18 mm Hg or no clinical evidence of diminished LV function.

**Diagnosis**

**Labs**
- ABGs: initially, varying degrees of hypoxemia, generally resistant to supplemental oxygen; subsequently, respiratory alkalosis, ↓ PCO2, and widened alveolar-arterial gradient. Hypercapnia occurs as the disease progresses.
- Hemodynamic monitoring (when indicated): although no hemodynamic profile is diagnostic of ARDS, the presence of pulmonary edema, ↑ CO, and ↓ PAWP are characteristic of ARDS.

**Imaging**
- CXR: bilateral interstitial infiltrates are usually seen within 24 hr; they are often more prominent in the bases and periphery. Near-total “whiteout” of both lung fields can be seen in advanced stages.

**Etiology**
- Sepsis (>40% of cases)
- Aspiration: near-drowning, aspiration of gastric contents (>30% of cases)
- Trauma (>20% of cases)
- Multiple transfusions, blood products
- Drugs (e.g., OD of morphine, methadone, heroin; reaction to nitrofurantoin)
Noxious inhalation (e.g., chlorine gas, high O₂ concentration)
Post resuscitation
Cardiopulmonary bypass
Pneumonia, tuberculosis
Burns
Pancreatitis

**Treatment**
- Identification and Rx of precipitating condition:
  - Blood and urine cultures and trial of abx in presumed sepsis (routine administration of abx in all cases of ARDS is not recommended)
  - Stabilization of bone fx in pts w/major trauma
  - Bowel rest and crystalloid resuscitation in pancreatitis
- Ventilatory support: mechanical ventilation is generally necessary to maintain adequate gas exchange. AC is generally preferred initially w/the following ventilator settings:
  - Fio₂: 100% (until a lower value can be used to achieve adequate oxygenation). When possible, minimize oxygen toxicity by maintaining Fio₂ at <60%.
  - Tidal volume: set initial tidal volume at 6 mL/kg of BW. Aim to maintain plateau pressure (Pₚₚₚₚₚₚₚₚₚₚ) at <30 mm Hg.
  - PEEP: ≥5 cm H₂O (to ↑ lung volume and keep alveoli open)
  - Inspiratory flow: 60 L/min
  - Ventilatory rate: ↑ ventilatory rates of 18-24 breaths/min are often necessary in pts w/ARDS because of their ↑ physiologic dead space and smaller lung volumes.
- Fluid management: optimal fluid management is pt specific. Swan-Ganz catheterization may be indicated and is useful to guide fluid replacement. A PCWP of approximately 12 mm Hg is ideal.
- DVT prophylaxis
- Stress ulcer prophylaxis w/sucralfate suspension (by NG tube) or IV PPIs or IV H₂ blockers.

**Clinical Pearl**
- A prior h/o chronic alcohol abuse significantly ↑ the risk for development of ARDS in critically ill pts.

### 13 ACUTE TUBULAR NECROSIS (ATN)

**Definition**
Acute injury to the tubules of the kidneys. The term *tubulointerstitial nephropathy* refers to damage to the tubules and interstitium. Because these structures are intimately related, initial damage to either one generally progresses to affect the other.

**Diagnosis**

**Lab**
- Serial ↑ in Cr and BUN varies w/catabolic rate and protein intake.
- Oliguria or nonoliguria, but relatively fixed outputs
- Variable response to high-dose furosemide: may allow diuresis but does not change the underlying lesion
- Pulmonary vascular congestion and hyperkalemia represent the most important parameters to follow: pulmonary artery catheter may be necessary to monitor fluid status.
- Urinary sodium is ↑, generally >30.
- Urinary osmolarity is <350 mOsm/kg.
- Urinary Cr is ↓ in relation to urinary volume, leading to a U/P Cr level <20.
- FEna is >1.
- Urinary sediment contains “muddy brown” renal tubular casts.
- Myoglobinuria and serum CPK are ↑ in rhabdo.
- Polyuric phase often heralds healing.

**Etiology**
- Perfusional deficits (prolonged prerenal failure, shock, hypovolemia, sepsis, pancreatitis, low-output states, CABG surgery, aortic aneurysm repair)
- Pigment nephropathy: myoglobinuria (rhabdo), hemoglobinuria
Diseases resulting from inadequate secretion of corticosteroids of vitamin C

**H&P**

**Diagnosis**

The acute reductions in GFR lead to delta increases in Cr (2+ mg/day), a low U/P:Cr ratio (<20), oliguric or nonoliguric urinary volumes, threatening hyperkalemia, and pulmonary vascular congestion.

**Treatment**

Most pts w/ARF recover w/conservative management (fluid monitoring, protein restriction, drug adjustments, and dietary or Kayexalate potassium control).

Dialysis, usually temporary, may become necessary (see indications for dialysis).

Because the hemodynamic stress associated w/hemodialysis can be additionally detrimental to renal function, the decision to start dialysis must weigh the acute needs against anticipated stabilization.

Continuous hemofiltration (CVVH) or continuous hemodialysis (CVVHD) conceptually is preferable to intermittent dialysis in the unstable renal failure pt in the intensive care unit, but data are conflicting.

Given an intact peritoneal surface, acute percutaneous peritoneal dialysis can stabilize BUN/Cr and control fluid balance in selected pts.

**Clinical Pearl**

For prevention of ATN from radiocontrast, 1 L NS prior hydration is the best proven prophylactic measure. N-Acetylcysteine administration also reduces toxicity in high-risk pts.

**20 ADRENAL INSUFFICIENCY (ADDISON’S DISEASE)**

**Definition**

Disorder characterized by inadequate secretion of corticosteroids resulting from partial or complete destruction of the adrenal glands.

**Diagnosis**

**H&P**

Hyperpigmentation, hypotension, generalized weakness, amenorrhea, and loss of axillary hair in females

**Labs** (Fig. 3-7)

- Perform rapid ACTH (cosyntropin) test: 250 µg ACTH by IV push; measure cortisol level at 0, 30, 60 min. Cortisol level <18 µg/dL at 30 min or 60 min is suggestive of adrenal insufficiency. Measure plasma ACTH level: ↑ level indicates primary adrenal insufficiency, nl/↓ level indicates secondary adrenal insufficiency.
- ↑ K⁺, ↓ Na⁺ and Cl⁻, ↓ glucose, ↑ BUN/Cr ratio (prerenal azotemia), mild normocytic normochromic anemia, neutropenia, lymphocytosis, eosinophilia (significant dehydration may mask the hyponatremia and anemia), ↓ 24-hr urinary cortisol, 17-OHCS, and 17-KS and ↑ ACTH (if primary adrenocortical insufficiency).

**Etiology**

- Autoimmune destruction of the adrenals (80% of cases)
- TB (15% of cases)
- Carcinomatous destruction of the adrenals
- Adrenal hemorrhage (anticoagulants, trauma, coagulopathies, pregnancy, sepsis); adrenal infarction (arteritis, thrombosis)
- AIDS (adrenal insufficiency develops in 30% of pts w/advanced AIDS)
- Other: sarcoidosis, amyloidosis, postoperative, fungal infection, megestrol acetate Rx, etomidate Rx

**Treatment**

**Chronic Adrenocortical Insufficiency**

- Hydrocortisone, 15-20 mg PO q AM and 5-10 mg in late afternoon or prednisone 5 mg in AM and 2.5 mg at hs.
**ALCOHOL WITHDRAWAL**

**Definition**
Syndrome that occurs when a person stops ingesting alcohol after prolonged consumption. Sx vary according to the severity of the pt’s alcohol abuse and the time interval from the pt’s previous alcohol ingestion.

**Clinical Pearl**
Pts should be instructed to ↑ glucocorticoid replacement in times of stress and to receive parenteral glucocorticoids if diarrhea or vomiting occurs.

**Addisonian Crisis**
Acute complications of adrenal insufficiency characterized by circulatory collapse, dehydration, N/V, hypoglycemia, and hyperkalemia.

- Draw plasma cortisol level; do not delay Rx until confirming lab results are obtained.
- Administer hydrocortisone 50-100 mg IV q6h for 24 hr; if pt shows good clinical response, gradually taper dosage and change to PO maintenance dose (usually prednisone, 7.5 mg/day).
- Provide adequate volume replacement w/D5NS solution until hypotension, dehydration, and hypoglycemia are completely corrected. Large volumes (2-3 L) may be necessary in the first 2-3 hr to correct the volume deficit and hypoglycemia and to avoid further hyponatremia.
- Identify and correct any precipitating factor (e.g., sepsis, hemorrhage).

**Oral fludrocortisone 0.05-0.20 mg/day:** this mineralocorticoid replacement is necessary if the pt has primary adrenocortical insufficiency. The dose is adjusted on the basis of the serum sodium level and the presence of postural hypotension or marked orthostasis.

- Monitor serum electrolytes, VS, and BW periodically: advise liberal sodium intake.

- The administration of dehydroepiandrosterone 50 mg PO qd improves well-being and sexuality in women w/adrenal insufficiency.

**Suspected Addison’s disease**

**IV cosyntropin; measure cortisol level at baseline, 30 min, 60 min**

- ↑ cortisol level (>18 mcg/dL)
- ↓ cortisol level (<18 mcg/dL)

- No adrenal insufficiency
- ACTH level
- Normal ↓
- ↑

**Adrenal insufficiency secondary to pituitary insufficiency**

- Primary adrenal insufficiency

**FIGURE 3-7.** Diagnostic algorithm for adrenal insufficiency (Addison’s disease).
Diagnosis

- **Tremulous state** [early alcohol withdrawal, “impending delirium tremens,” “shakes,” “jitters”]
  - Time interval: usually occurs 6-8 hr after the last drink or 12-48 hr after reduction of alcohol intake; becomes most pronounced at 24-36 hr
  - Manifestation: tremors, mild agitation, insomnia, tachycardia; sx are relieved by alcohol

- **Alcoholic hallucinosis**: hallucinations are usually auditory, but occasionally hallucinations are visual, tactile, or olfactory; usually there is no clouding of sensorium as in delirium (clinical presentation may be mistaken for an acute schizophrenic episode). Disordered perceptions become most pronounced after 24-36 hr of abstinence.

- **Withdrawal seizures (“rum fits”)**
  - Time interval: usually occurs 7-30 hr after cessation of drinking, w/a peak incidence between 13-24 hr.
  - Manifestations: generalized convulsions w/loss of consciousness; focal signs are usually absent; consider further investigation w/CT scan of head and EEG if clearly indicated (e.g., presence of focal neurologic deficits, prolonged postictal confusion state). In addition, in a febrile pt who is having a seizure or ΔMS, an LP may be necessary.

- **Delirium tremens (DTs)**
  - Time interval: variable; usually occurs within 1 wk after reduction or cessation of heavy alcohol intake and persists for 1-3 days. Peak incidence is 72 and 96 hr after the cessation of alcohol consumption.
  - Manifestations: profound confusion, tremors, vivid visual and tactile hallucinations, autonomic hyperactivity; this is the most serious clinical presentation of alcohol withdrawal (mortality is approximately 15% in untreated pts).

Treatment

- Inpatient treatment
  - Admit to medical ward (private room); monitor VS q4h; institute seizure precautions; maintain adequate sedation.
  - Administer lorazepam as follows:
    - In pts w/DTs, initially lorazepam 2-5 mg IM/IV repeated PRN. In stable pts, oral administration may be sufficient: day 1, 2 mg PO q4h while awake and not lethargic; day 2, 1 mg PO q4h while awake and not lethargic; day 3, 0.5 mg PO q4h while awake and not lethargic.
    - In pts w/mild to moderate withdrawal and w/o h/o seizures, individualized benzo administration (rather than a fixed-dose regimen) results in lower benzo administration and avoids unnecessary sedation. The Clinical Institute Withdrawal Assessment—Alcohol (CIWA-A) scale can be used to measure the severity of alcohol withdrawal. It consists of the 10 following items: nausea; tremor; autonomic hyperactivity; anxiety; agitation; tactile, visual, and auditory disturbances; headache; and disorientation. The maximum score is 67. When the CIWA-A score is ≥8, pts are usually given 2-4 mg of lorazepam hourly.
  - Dexmedetomidine (Precedex) can also be used for sedation in ICU:
    - Adults 1 µg/kg over 10 min; adjust in the elderly
    - Maintenance of intensive care sedation: 0.2-0.7 µg/kg/hr to achieve desired level of sedation
  - β-Blockers: useful for controlling BP and tachyarrhythmias. However, they do not prevent progression to more serious sx of withdrawal and, if used, should not be administered alone but in conjunction w/benzos. β-Blockers should be avoided in pts w/contraindications to their use (e.g., bronchospasm, bradycardia).
  - Vitamin replacement: thiamine 100 mg IV or IM for at least 5 days, plus PO multivitamins. The IV administration of glucose can precipitate Wernicke’s encephalopathy in alcoholics w/thiamine deficiency; therefore, thiamine administration should precede IV dextrose.
  - Hydration PO or IV (high-calorie solution); if IV: glucose w/Na+, K+, Mg2+, and phosphate replacement PRN.
Withdrawal seizures can be treated w/diazepam 2.5 mg/min IV until seizure is controlled (check for respiratory depression or hypotension); IV lorazepam 1-2 mg q2h can be used in place of diazepam; generally, withdrawal seizures are self-limited and treatment is not required; the use of phenytoin or other anticonvulsants for short-term treatment of alcohol withdrawal seizures is not recommended.

**Clinical Pearl**

Blood ethanol level ↓ by 20 mg/dL/hr in a nl 70-kg person.

### 22. ALKALOSIS, METABOLIC

**Definition**

Disturbance of acid-base balance. The primary event is an elevation of the plasma HCO₃⁻ concentration.

**Diagnosis**

Evaluate type of disturbance present by examining pH, PCO₂, and HCO₃⁻ (Fig. 3-8).

![Diagnostic algorithm for metabolic alkalosis.](image)

**Etiology**

- Divided into chloride-responsive (urinary chloride <15 mEq/L) and chloride-resistant (urinary chloride level >15 mEq/L) forms

**Chloride Responsive**

- Vomiting
- NG suction
- Diuretics
- Post hypercapnic alkalosis
- Stool losses (laxative abuse, cystic fibrosis, villous adenoma)
- Massive blood transfusion
- Exogenous alkali administration
Chloride Resistant
- Hyperadrenocorticoid states (Cushing’s syndrome, primary hyperaldosteronism, secondary mineralocorticoidism [licorice, chewing tobacco])
- Hypomagnesemia
- Hypokalemia
- Bartter’s syndrome

Treatment
- Chloride-responsive forms: Rx w/saline administration and correction of accompanying hypokalemia
- Chloride-resistant forms: correct underlying cause and associated potassium depletion

Clinical Pearl
- An ↑ in HCO₃⁻ by 1 will ↑ pH by 0.015 and ↑ PaCO₂ by 0.7. The compensatory response (↑ PaCO₂) is usually limited to a max PaCO₂ of 55. There is an impaired compensatory response in pts w/COPD, heart failure, and hepatic coma.

23 ALKALOSIS, RESPIRATORY

Definition
Disturbance of acid-base balance characterized by a primary ↓ in PCO₂.

Diagnosis
- Evaluate type of disturbance present by examining pH, PCO₂, and HCO₃⁻ (Fig. 3-9).

Serum electrolytes, ABGs
↑pH, ↑PaCO₂
Respiratory alkalosis
Determine if acute or chronic by evaluating degree of compensation

Chronic: A ↓ in PaCO₂ by 10 will ↑ pH by 0.03 and ↓ HCO₃⁻ by 5
Acute: A ↓ in PaCO₂ by 10 will ↑ pH by 0.08 and ↓ HCO₃⁻ by 2.5

FIGURE 3-9. Diagnostic algorithm for respiratory alkalosis.

Etiology
- Hypoxemia (pneumonia, PE, atelectasis, high-altitude living)
- Drugs (salicylates, xanthines, progesterone, epinephrine, thyroxine, nicotine)
- CNS disorders (tumor, CVA, trauma, infections)
- Psychogenic hyperventilation (anxiety, hysteria)
- Hepatic encephalopathy
- Gram-negative sepsis
- Hyponatremia
- Sudden recovery from metabolic acidosis
- Assisted ventilation
Diseases

AAT DEFICIENCY

H&P

Diagnosis

Treatment

Clinical Pearls

In acute respiratory alkalosis, a ↓ in Paco2 by 10 will ↑ pH by 0.08 and ↓ HCO3 by 2.5.

In chronic respiratory alkalosis, a ↓ in Paco2 by 10 will ↑ pH by 0.03 and ↓ HCO3 by 5.

24 ALPHA1-ANTITRYPsin DEFICIENCY (AAT DEFICIENCY)

Definition

Diagnosis

H&P

Labs

Imaging

Etiology

Degree of AAT deficiency is dependent on phenotype. MM represents the nl genotype and is associated w/AAT in the nl range. Mutation most commonly associated w/emphysema is Z, w/homozygote (ZZ) resulting in approximately 85% deficit in plasma alpha1-antitrypsin concentrations.

Treatment

Acute exacerbations of COPD secondary to AAT deficiency are treated in similar fashion to “typical” COPD exacerbations

IV administration of pooled human alpha1-antitrypsin can be used once/wk (60 mg/kg) to raise alpha1-antitrypsin levels above a minimum, “protective” threshold (11 μM).

Surgical options: lung volume reduction, lung transplantation, lung and liver transplantation

Clinical Pearl

Consider AAT deficiency in pts presenting w/lower lobe–predominant emphysema because in most smokers w/o AAT deficiency, emphysema predominates in the upper lobes.

25 ALTITUDE SICKNESS

Definition

Diagnosis

H&P

Labs

Imaging

CXR: Kerley B lines and patchy edema in high-altitude pulmonary edema

CT scan of head reveals diffuse or patchy edema in high-altitude cerebral edema.
AMAUROSIS FUGAX

**Definition**
Temporary loss of monocular vision caused by transient retinal ischemia.

**Diagnosis**

- **H&P**
  - Examine retina for presence of embolus, auscultate carotids for bruits, evaluate for temporal artery tenderness (r/o GCA), examine for signs of hemispheric stroke (contralateral limb and face weakness or sensory loss, aphasia, ...).

- **Labs**
  - CBC, ESR, lipid panel, ANA. Hypercoagulable w/u is discretionary on the basis of younger age and hx.

- **Imaging**
  - Carotid Dopplers followed by MRA or four-vessel angiography
  - TTE when cardiac sources of embolization (ventricular mural thrombus, atrial appendage, patent foramen ovale, aortic arch) are suspected
  - Consider MRI of the brain w/diffusion-weighted imaging

**Etiology**

- Usually embolic from the internal carotid artery or the heart but may also be due to vasculitis, such as GCA, or hyperviscosity syndromes, such as sickle cell disease, that cause ischemia in the vascular territory of the ophthalmic artery

**Treatment**

- ASA if etiology is presumed embolic
- If GCA is suspected, start prednisone and refer for temporal artery bx within 48 hr
- Carotid endarterectomy or stenting if degree of stenosis exceeds 70%
- Control HTN and manage vascular risk factors, avoid tobacco
- Antiplatelet Rx
- Statin in hyperlipidemic pts

**Clinical Pearl**

- Among pts w/>50% carotid stenosis who do not undergo carotid endarterectomy, those who present w/transient monocular blindness have about a 10% risk of stroke in 3 yr compared w/a 20% risk in pts who present w/a hemispheric TIA.
27 AMEBIASIS

Definition
Infection primarily of the colon caused by the protozoal parasite *Entamoeba histolytica*. Transmission by the fecal-oral route. Infection usually localized to the large bowel, particularly the cecum, where a localized mass lesion (ameboma) may form. Extraintestinal infection in which the organism invades the bowel mucosa and gains access to the portal circulation.

Diagnosis

**H&P**
- Clinical presentation: often nonspecific; approximately 20% of cases symptomatic
- Diarrhea, which may be bloody
- Abd and back pain
- Abd tenderness in 83% of severe cases
- Fever in 38% of severe cases
- Hepatomegaly, RUQ tenderness, and fever in almost all pts w/liver abscess (may be absent in fulminant cases)

**Labs**
- Stool exam for parasite is generally reliable. Three stool specimens during a period of 7-10 days exclude the diagnosis (sensitivity 50%-80%).
- Mucosal bx is occasionally necessary.
- Serum Ab may be detected and is particularly sensitive and specific for extraintestinal infection or severe intestinal disease.
- Aspiration of abscess fluid is used to distinguish amebic from bacterial abscesses.

**Imaging**
- Abd U/S or CT scan

Treatment
- Metronidazole (750 mg PO or IV tid for 10 days) is used in the treatment of mild to severe intestinal infection and amebic liver abscess.
- Follow with iodoquinol (650 mg PO tid for 20 days) to eradicate persistent cysts.
- For asymptomatic pts w/amebic cysts on stool exam, use iodoquinol or paromomycin (500 mg PO tid for 7 days).
- Avoid antiperistaltic agents in severe intestinal infections to avoid risk of toxic megacolon.
- Liver abscess is generally responsive to medical management, but surgical intervention is indicated for extension of liver abscess into pericardium or, occasionally, for toxic megacolon.

28 AMPHETAMINE OVERDOSE

Diagnosis

**H&P**
- Tachycardia, HTN, mydriasis, agitation, seizures, diaphoresis, psychosis, hyperthermia

**Labs**
- Lytes, BUN, Cr, CPK

Treatment
- Activated charcoal
- Gastric lavage for acute large ingestion
- Sedation w/benzos (diazepam)
- Haloperidol for hallucinations and psychosis
- Propranolol or lidocaine for arrhythmias

Clinical Pearl
- Induction of emesis is contraindicated.

29 AMYOTROPHIC LATERAL SCLEROSIS

Definition
Progressive, degenerative neuromuscular condition affecting corticospinal tracts and anterior horn cells resulting in dysfunction of both UMN's and LMN's, respectively.
Diseases and Disorders

**Diagnosis**

**H&P**
- LMN signs (weakness, hypotonia, wasting, fasciculations, hyporeflexia or areflexia)
- UMN signs (loss of fine motor dexterity, spasticity, extensor plantar responses, hyperreflexia, clonus)
- Preservation of extraocular movements, sensation, bowel and bladder function
- Dysarthria, dysphagia, pseudobulbar affect, frontal lobe dysfunction

**Labs**
- LP to assess protein, serum GM₁ Ab if multifocal motor neuropathy suspected
- B₁₂, thyroid function, serum calcium, albumin, HIV may be considered
- Serum protein and immunofixation electrophoresis
- DNA studies for spinal muscular atrophy or bulbospinal atrophy; hexosaminidase levels in pure LMN syndrome
- 24-hr urine for lead if indicated by hx

**Imaging**
- Craniospinal neuroimaging contingent on clinical scenario
- Modified barium swallow to evaluate aspiration risk
- Assessment of respiratory function (FVC, negative inspiratory force)
- EMG and nerve conduction studies

**Etiology**
- 90%-95% of all cases are sporadic; of the familial cases, approximately 20% are associated w/ a genetic defect in the copper-zinc superoxide dismutase enzyme (SOD1).

**Treatment**
- NIPPV improves quality of life and ↑ tracheostomy-free survival.
- Percutaneous endoscopic gastrostomy (PEG) placement improves calorie and fluid status, eases medication administration, and may prolong life on the order of 1-4 mo.
- Nutrition, speech Rx, physical and occupational Rx services
- Suction device for sialorrhea
- Communication may be eased w/computerized assistive devices.
- Early discussion of living will, resuscitation orders, desire for PEG and tracheostomy, potential long-term care options
- Consider riluzole in selected pts.
- Relief of spasticity w/baclofen, clonazepam
- Rx of pseudobulbar affect w/amitriptyline, sertraline, dextromethorphan

**Clinical Pearl**
- GI referral for PEG placement is recommended while FVC remains >50% to minimize the risks inherent to the procedure.

**ANAPHYLAXIS**

**Definition**
Sudden-onset, life-threatening event characterized by bronchial contractions in conjunction w/ hemodynamic changes. Its clinical presentation may include respiratory, CV, cutaneous, or GI manifestations.

**Diagnosis**

**H&P**
- Urticaria, pruritus, skin flushing, angioedema, weakness
- Dizziness, dyspnea, cough, malaise, difficulty swallowing, wheezing
- Tachycardia, diarrhea
- Hypotension, vascular collapse

**Labs**
- Laboratory evaluation is generally not helpful because the diagnosis of anaphylaxis is a clinical one.
- W/u is aimed mainly at eliminating other conditions that may mimic anaphylaxis (e.g., vasovagal syncope may be differentiated by the presence of bradycardia as opposed to the tachycardia seen in anaphylaxis; the absence of hypoxemia in ABG analysis may be useful to exclude PE or foreign body aspiration).
Etiology
- Virtually any substance may induce anaphylaxis in a given individual.
- Commonly implicated medications are abx, insulin, allergen extracts, opiates, vaccines, NSAIDs, contrast media, streptokinase.
- Foods and food additives, nuts, egg whites, shellfish, fish, milk, fruits, and berries
- Blood products, plasma, immunoglobulin, cryoprecipitate, whole blood
- Venoms such as snake venom, fire ant venom, bee sting (Hymenoptera stings)
- Latex

Treatment
- IV fluids (NS); establish and protect airway; place pt in supine or Trendelenburg position; supplemental oxygen, cardiac monitoring
- Epinephrine SC or IM injection at a dose of 0.01 mL/kg of aqueous epinephrine 1:1000 (maximum adult dose 0.3-0.5 mL). The dose may be repeated approximately q5-10min if there is persistence or recurrence of sx. Endotracheal epinephrine should be considered if IV access is not possible during life-threatening reactions.
- H₁ and H₂ receptor antagonists
- Diphenhydramine 50-75 mg IV or IM
- Cimetidine 300 mg IV during 3-5 min, or ranitidine 50 mg IV initially; subsequent doses of H₁ and H₂ blockers can be given PO q6h for 48 hr.
- Corticosteroids: not useful in the acute episode because of their slow onset of action; however, they should be administered in most cases to prevent prolonged or recurrent anaphylaxis. Commonly used agents are hydrocortisone sodium succinate 250-500 mg IV q4-6h in adults (4-8 mg/kg for children) and methylprednisolone 60-125 mg IV in adults (1-2 mg/kg in children).
- Aerosolized β-agonists (i.e., albuterol, 2.5 mg; repeat PRN 20 min): useful to control bronchospasm
- Additional agents in specific circumstances: atropine for refractory bradycardia, dopamine for refractory hypotension (despite volume expansion), and glucagon in pts taking β-blocking drugs

Clinical Pearl
- Prescription for prefilled epinephrine syringe (EpiPen) should be given, and the pt should be instructed on the use of this emergency epinephrine kit in case of recurrent anaphylactic episodes.

31 ANEMIA, APLASTIC

Definition
Bone marrow failure resulting from a variety of causes and characterized by stem cell destruction or suppression leading to pancytopenia.

Diagnosis

Labs
- Diagnostic w/u consists primarily of bone marrow aspiration and bx and laboratory evaluation (CBC and examination of blood film).
- CBC: pancytopenia. Macrocytosis and toxic granulation of neutrophils may also be present. Isolated cytopenias may occur in the early stages.
- Reticulocyte count: reticulocytopenia
- Additional initial laboratory evaluation should include Ham test to exclude PNH and testing for HCV.
- Bone marrow examination: paucity or absence of erythropoietic and myelopoietic precursor cells; pts w/pure red cell aplasia demonstrate only absence of RBC precursors in the marrow.

Imaging
- U/S or CT of abd to evaluate for splenomegaly
- CT scan of thymus region if thymoma-associated RBC aplasia is suspected

Etiology
- In most pts w/acquired aplastic anemia, bone marrow failure results from immunologically mediated, active destruction of blood-forming cells by lymphocytes.
Common etiologic factors in aplastic anemia:
- Toxins (e.g., benzene, insecticides)
- Drugs (e.g., felbamate, cimetidine, busulfan and other myelosuppressive
drugs, gold salts, chloramphenicol, sulfonamides, trimethadione,
quinacrine, phenylbutazone)
- Ionizing irradiation
- Infections (e.g., HCV, HIV)
- Idiopathic
- Inherited (Fanconi’s anemia)
- Other: immunologic, pregnancy

**Treatment**
- Rx of neutropenic fevers w/parenteral broad-spectrum abx
- Platelet and RBC transfusions PRN; however, avoidance of transfusions
in pts who are candidates for bone marrow transplantation
- Immunosuppressive Rx w/antithymocyte globulin (ATG) or cyclosporine
(CSP); ATG in combination w/prednisone (1-2 mg/kg/day initially) to avoid
complications of serum sickness
- Transplantation of allogeneic marrow or peripheral blood SCT from a
histocompatible sibling usually cures the underlying bone marrow failure.
- In pts w/severe aplastic anemia who are not candidates for allogeneic bone
marrow, use of high-dose cyclophosphamide Rx w/o bone marrow
transplantation represents a third treatment option for initial treatment of
aplastic anemia.

**Clinical Pearls**
- ATG w/CSP restores hematopoiesis in approximately two thirds of pts;
however, recovery of blood cell count is often incomplete, recurrent
pancytopenia requires re-treatment. In some pts, myelodysplasia is a late
complication of immunosuppressive Rx.
- Response to immunosuppression in aplastic anemia is independent of age,
but treatment is associated w/↑ mortality in older pts.

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**ANEMIA, AUTOIMMUNE HEMOLYTIC**

**Definition**
Anemia secondary to premature destruction of RBCs caused by the binding of
auto-Abs or complement to RBCs.

**Diagnosis**

**H&P**
- Pallor, jaundice
- Tachycardia w/flow murmur if anemia is pronounced
- Dyspnea and fatigue: most common presentation
- Pts w/intravascular hemolysis may present w/dark urine and back pain.
- Presence of hepatomegaly or lymphadenopathy suggests an underlying
lymphoproliferative disorder or malignant neoplasm.
- Splenomegaly may indicate hypersplenism as a cause of hemolysis.

**Labs**
- Initial labs: CBC (anemia), reticulocyte count (↑), liver function studies
(↑ indirect bili, LDH), evaluation of peripheral smear, Coombs’ test
(+ direct Coombs’ test indicates presence of Abs or complement on
the surface of RBC; + indirect Coombs’ test implies presence of anti-RBC
Abs freely circulating in the pt’s serum), haptoglobin level (↓)
- IgG Ab and IgM Ab
- Hepatitis serology, ANA, HIV
- U/A: hemosiderinuria or hemoglobinuria

**Imaging**
- CXR
- CT of chest and abd: r/o lymphoma

**Etiology**
- Warm Ab-mediated: IgG (often idiopathic or associated w/leukemia,
lymphoma, thymoma, myeloma, viral infections, and collagen-vascular
disease)
Anemia

**Definition**

Anemia secondary to inadequate iron supplementation or excessive blood loss.

**Diagnosis**

**H&P**

- Fatigue, dizziness, exertional dyspnea, pagophagia (ice eating), pica. Pt’s hx may also suggest GI blood loss (melena, hematochezia, hemoptysis).

**Labs**

- Lab results vary w/the stage of deficiency.
- Absent iron marrow stores and ↓ serum ferritin are the initial abnormalities.
- ↓ Serum iron and ↑ TIBC are the next abnormalities.
- Hypochromic microcytic anemia is present w/significant iron deficiency.
- Peripheral smear in pts w/iron deficiency generally reveals microcytotic hypo chromic RBCs w/a wide area of central pallor, anisocytosis, and poikilocytosis when severe.
- Lab abnormalities consistent w/iron deficiency are ↓ serum ferritin level, ↑ RDW w/values generally <15, ↓ MCV, ↑ TIBC, and ↓ serum iron.

**Etiology**

- Blood loss from GI or menstrual bleeding (GU blood loss less often the cause)
- Dietary iron deficiency (rare in adults)
- Poor iron absorption in pts w/gastric or small bowel surgery
- Repeated phlebotomy
- ↑ Requirements (e.g., during pregnancy)
- Other: traumatic hemolysis (abnormally functioning cardiac valves), idiopathic pulmonary hemosiderosis (iron sequestration in pulmonary macrophages), PNH (intravascular hemolysis)

**Treatment**

- Ferrous sulfate 325 mg PO qd-tid for at least 6 mo. Ca²⁺ supplements can ↓ iron absorption; therefore, these two medications should be staggered.
- Parenteral iron Rx: reserved for pts w/poor tolerance, noncompliance w/oral preparations, or malabsorption.

### Chapter 3 Diseases and Disorders

- Cold Ab mediated: IgM and complement in majority of cases (often idiopathic, at times associated w/infections, lymphoma, or cold agglutinin disease)
- Drug induced: three major mechanisms:
  - Ab directed against Rh complex (e.g., methyldopa)
  - Ab directed against RBC drug complex (hapten induced, e.g., PCN)
  - Ab directed against complex formed by drug and plasma proteins; the drug–plasma protein–Ab complex causes destruction of RBCs (innocent bystander, e.g., quinidine)

**Treatment**

- Prednisone 1-2 mg/kg/day in divided doses initially in warm Ab AIHA. Corticosteroids are generally ineffective in cold Ab AIHA.
- Splenectomy in pts responding inadequately to corticosteroids when RBC sequestration studies indicate splenic sequestration
- Immunosuppressive drugs or immunoglobulins only after both corticosteroids and splenectomy (unless surgery is contraindicated) have failed to produce an adequate remission
- Danazol, usually used in conjunction w/corticosteroids (may be useful in warm Ab AIHA)
- Immunosuppressive drugs (azathioprine, cyclophosphamide) may be useful in warm Ab AIHA but are indicated only after both corticosteroids and splenectomy (unless surgery is contraindicated) have failed to produce an adequate remission.

**Clinical Pearl**

- Avoid cold exposure in pts w/cold Ab.

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**35 ANEMIA, IRON DEFICIENCY**

**Definition**

Anemia secondary to inadequate iron supplementation or excessive blood loss.

**Diagnosis**

**H&P**

- Fatigue, dizziness, exertional dyspnea, pagophagia (ice eating), pica. Pt’s hx may also suggest GI blood loss (melena, hematochezia, hemoptysis).

**Labs**

- Lab results vary w/the stage of deficiency.
- Absent iron marrow stores and ↓ serum ferritin are the initial abnormalities.
- ↓ Serum iron and ↑ TIBC are the next abnormalities.
- Hypochromic microcytic anemia is present w/significant iron deficiency.
- Peripheral smear in pts w/iron deficiency generally reveals microcytotic hypochromic RBCs w/a wide area of central pallor, anisocytosis, and poikilocytosis when severe.
- Lab abnormalities consistent w/iron deficiency are ↓ serum ferritin level, ↑ RDW w/values generally <15, ↓ MCV, ↑ TIBC, and ↓ serum iron.

**Etiology**

- Blood loss from GI or menstrual bleeding (GU blood loss less often the cause)
- Dietary iron deficiency (rare in adults)
- Poor iron absorption in pts w/gastric or small bowel surgery
- Repeated phlebotomy
- ↑ Requirements (e.g., during pregnancy)
- Other: traumatic hemolysis (abnormally functioning cardiac valves), idiopathic pulmonary hemosiderosis (iron sequestration in pulmonary macrophages), PNH (intravascular hemolysis)

**Treatment**

- Ferrous sulfate 325 mg PO qd-tid for at least 6 mo. Ca²⁺ supplements can ↓ iron absorption; therefore, these two medications should be staggered.
- Parenteral iron Rx: reserved for pts w/poor tolerance, noncompliance w/oral preparations, or malabsorption.
Transfusion of PRBCs is indicated in pts w/severe symptomatic anemia (e.g., angina) or life-threatening anemia.

Clinical Pearls
- Dietary iron deficiency occurs often in infants as a result of unsupplemented milk diets. It is also commonly seen in women during their reproductive years, as a result of heavy menstrual periods, and during pregnancy (↑ demand).
- If the diagnosis of iron deficiency anemia is made, it is mandatory to try to locate the suspected site or etiology of iron loss.

34 ANEMIA, MACROCYTIC

Definition
Anemia characterized by macrocytic features of RBCs (elevated MCV). “Megaloblastic anemias” refer to morphologic abnormalities of cell nuclei caused by various defects in DNA synthesis.

Diagnosis
Labs (Fig. 3-10)
- Serum vitamin B₁₂ level: a ↓ level indicates vitamin B₁₂ deficiency; exceptions are falsely ↓ levels seen in pts w/severe folate deficiency or falsely ↑ N levels when vitamin B₁₂ deficiency coincides w/severe liver disease or CLL.
- Serum folate, RBC folate: both tests should be ordered because serum folate alone is labile and does not accurately reflect tissue folate levels, whereas RBC folate is a good indicator of tissue stores but may be reduced in severe cobalamin (Cbl) deficiency.
- Peripheral blood smear: hypersegmented neutrophils (>6 lobes) are present in vitamin B₁₂ and folate deficiency.
- Macro-ovalocytes
- Reticulocyte count: ↑ w/recent hemolysis
- TSH, ALT, AST: hypothyroidism and liver disease can ↑ MCV
- Bone marrow examination: megaloblastic erythroid hyperplasia

Macrocytic anemia

Reticulocyte count

Normal

Ancillary labs

Inconclusive

R/o blood loss

Diagnostic

Stool for OB × 3

R/o hemolysis

Coombs’ test

R/o alcohol abuse

Bone marrow exam

FIGURE 3-10. Diagnostic algorithm for macrocytic anemia.

Etiology
- Folate deficiency
  - ↓ Intake (alcoholism, poor diet)
  - ↑ Requirements (hemolysis, pregnancy, dialysis, leukemia, exfoliative dermatitis)
• Impaired absorption (e.g., sprue, IBD, ethanol)
• Drugs (e.g., phenytoin, MTX, ethanol, trimethoprim, antituberculous agents)
• Defective folate interconversion

■ Vitamin B₁₂ deficiency
  • Pernicious anemia (Abs against intrinsic factor and gastric parietal cells)
  • Dietary (strict lacto-ovo vegetarians, food faddists)
  • Malabsorption (achlorhydria, gastrectomy, ileal resection, Crohn’s disease of terminal ileum, pancreatic insufficiency, drugs [omeprazole, metformin, cholestyramine])
  • Chronic alcoholism (multifactorial)
  • H. pylori infection

■ Chronic liver disease (the ↑ MCV is multifactorial: ineffective erythropoiesis, hemolysis, acute blood loss)
■ Alcoholism (RBC membrane abnormalities)
■ Hypothyroidism (can also cause a normochromic normocytic anemia or hypochromic microcytic anemia)
■ ↑ Reticulocyte count (each ↑ in the reticulocyte count by 1% ↑ the MCV by approximately 2 fl)
■ Some pts w/aplastic anemia, myelodysplastic syndrome, or sideroblastic anemia may have macrocytic indices.
■ Myelodysplastic syndromes (stem cell disorders characterized by refractory cytopenias, ineffective hematopoiesis, and variable progression to acute myeloid leukemia)
■ Drugs that impair DNA synthesis: zidovudine, 5-FU, hydroxyurea, 6-mercaptopurine

Treatment
■ Folate deficiency: folic acid, 1 mg PO qd
■ Vitamin B₁₂ deficiency: traditional Rx of Cbl deficiency consists of IM injections of 1000 µg weekly for the initial 4-6 wk followed by 1000 µg/mo IM indefinitely

Clinical Pearl
■ Oral Cbl (1000 µg/day) is a safe, effective, and inexpensive replacement alternative in most pts after vitamin B₁₂ levels have been normalized, provided nl Cbl levels are ensured w/periodic serum measurements. Oral Rx can be effective also in mild cases of pernicious anemia because about 1% of an oral dose is absorbed by passive diffusion, a pathway that does not require intrinsic factor.

ANEMIA, MICROCYTIC

Definition
Anemia w/a reduced MCV.

Diagnosis (Fig. 3-11)

Peripheral Blood Smear
■ Iron deficiency: microcytic, hypochromic RBCs w/a wide area of central pallor; anisocytosis, and poikilocytosis when severe
■ Chronic disease: normocytic or macrocytic RBCs
■ Sideroblastic anemia: dimorphic population of cells (hypochromic cells and normochromic, normocytic cells); basophilic stippling may also be present
■ Thalassemia: basophilic stippling, target cells, high RBC count
■ Lead poisoning: basophilic stippling
■ Serum ferritin: reflects the quantity of stored iron:
  • ↓ level is diagnostic of iron deficiency.
  • NI↓ level does not r/o iron deficiency because ferritin is an acute-phase reactant and can be ↑ in the presence of infection, inflammation, or liver disease.
■ ↓ serum iron and ↑ TIBC are suggestive of iron deficiency anemia.
■ Reticulocyte count: ↑ w/acute blood loss or hemolysis
■ RDW: <15 is indicative of iron deficiency.
■ The reticulocyte Hb content (CHR) is also an excellent screening test for iron deficiency. It can be measured on an automated hematology analyzer
and represents a relatively inexpensive and fast way to detect iron deficiency.

- sEPO level is useful in the evaluation and treatment of anemia of chronic disease.

**Bone Marrow Examination**
- Iron deficiency: absent iron stores, absent sideroblasts
- Chronic disease: nl or ↑ iron stores, absent or ↓ sideroblasts
- Sideroblastic anemia: nl or ↑ iron stores, “ringed” sideroblasts present
- Thalassemia: nl or ↑ iron stores, nl or ↑ sideroblasts

**Etiology**
- Iron deficiency
- Chronic disease
- Sideroblastic anemia
- Thalassemia
- Lead poisoning

**Treatment**
- Iron deficiency anemia: ferrous sulfate, 325 mg PO qd-tid for at least 6 mo
- Chronic disease states: identification and Rx of underlying disease
- Sideroblastic anemia: Rx of the underlying disorder; some primary sideroblastic anemias may respond to oral pyridoxine (vitamin B₆), 100 mg PO tid
- Thalassemia: the major points in the management of homozygous thalassemia are as follows:
  - Periodic transfusions to maintain Hb at approximately 10 g/dL
  - Chelation Rx with deferoxamine mesylate to achieve negative iron balance
  - Splenectomy at age 5-10 yr
  - Ancillary measures (folic acid, vitamin C)
- Lead poisoning: children w/lead levels of 45-69 µg/dL should receive chelation Rx with succimer (DMSA) or edetate Ca disodium (CaNaEDTA). Use of both agents is indicated when blood lead levels exceed 69 µg/dL.
Clinical Pearls
- The reticulocyte count should be viewed in relation to the degree of anemia; a frequently used correction method is the determination of the reticulocyte production index (RPI):
  - RPI = (measured Hct/nl Hct) × reticulocyte count/maturation factor
- The maturation factor (MF) = 1 if the pt’s Hct is 45. Each 10-point ↓ in the pt’s Hct will ↑ the MF by 0.5 (e.g., if the pt’s Hct is 35, the MF is 1.5).
- The RPI subdivides anemias into two major classes:
  - RPI > 3: proliferative anemia (hemolysis, hemorrhage, response to hematetic agents)
  - RPI < 3: hypoproliferative anemia (marrow failure, iron deficiency, renal failure, endocrinopathies)

36 ANEMIA, NORMOCYTIC

Definition
Anemia w/nl MCV.

Diagnosis
Peripheral Blood Smear
- Hemolysis: findings vary w/the cause of the hemolysis
  - Helmet cells, schistocytes: microangiopathic hemolysis
  - Sickle cells, Howell-Jolly bodies: sickle cell anemia
  - RBC fragments in pt w/a mechanical heart valve: traumatic hemolysis
  - Spherocytes: hereditary spherocytosis, AIHAs
  - Spur cells (very irregular borders w/thorny projections): hepatic cirrhosis
- Aplastic anemia: neutropenia, thrombocytopenia (unless pure red cell aplasia is present)
- Myelophthisis: the peripheral smear shows a leukoerythroblastic picture (normoblasts, granulocyte precursors) caused by premature release from bone marrow

Labs
- Reticulocyte count: ↑ w/RBC destruction (hemolysis), ↓ w/RBC underproduction (e.g., aplastic anemia, myelophthisis)
- Coombs’ test
  - Direct: detects the presence of Ab or complement on the surface of RBCs
  - Indirect: detects the presence of anti-RBC Abs freely circulating in the pt’s serum
- LDH: ↑ in pt w/intravascular or extravascular hemolysis
- Haptoglobin: a serum protein that binds Hb; the Hb-haptoglobin complex is then cleared by the liver; ↓ haptoglobin indicates intravascular hemolysis.
- Indirect bili: ↑ in both intravascular and extravascular hemolysis
- Urinary hemosiderin and urinary Hb: detected in moderate to severe intravascular hemolysis
- Chromium Cr 51 red cell survival: expensive and difficult test; it should not be done as part of the initial evaluation of hemolytic anemias.
- Additional studies depend on clinical presentation: BUN, Cr (to r/o renal failure), and TSH; osmotic fragility test confirms dx of hereditary spherocytosis.

Bone Marrow Examination
- Aplastic anemia: scarcity or absence of erythropoietic and myelopoietic precursor cells; pts w/pure red cell aplasia demonstrate only absence of RBC precursors in the marrow
- Myelophthisis: replacement of nl marrow w/fibrosis, granulomas, or tumor cells (lymphoma, leukemia, metastatic carcinoma)

Etiology
- Hemolysis
- Aplastic anemia
- Acute hemorrhage (GI, GU), phlebotomy
- Renal failure
- Myelophthisis (marrow replacement by fibrosis, tumor, or granulomatous substance)
Chapter 3  Diseases and Disorders

- Combined microcytic and macrocytic anemia (e.g., iron and folate deficiency)
- Endocrine disorders (hypothyroidism, gonadal dysfunction, adrenal insufficiency)
- Chronic disease (connective tissue disorders, infection, cancer)
- Lead poisoning

**Treatment**
- Varies w/specific cause

### 37 ANEMIA OF CHRONIC DISEASE (ACD)

**Definition**
Anemia secondary to chronic illness. It is caused by several mechanisms (e.g., ↓ erythrocyte survival, ↑ uptake and retention of iron within cells of the reticuloendothelial system, inadequate transfer of iron from reticuloendothelial system, limited availability of iron for erythroid progenitor cells, iron-restricted erythropoiesis).

**Diagnosis**
- Labs
  - Relatively mild Hb (usually >10 g/L), normochromic, normocytic, or microcytic anemia. The dx of ACD is primarily one of exclusion.
  - ↓ Iron and transferrin saturation, ↓ TIBC, and N↑ ferritin level. ↓ Reticulocyte index. Where available, a ↓ ratio (<1) of soluble transferrin receptor to the log of the ferritin level suggests ACD, whereas a ↑ ratio (>2) indicates iron deficiency anemia or coexistence of both conditions.

**Etiology**
ACD is often seen in pts w/chronic infections (e.g., tuberculosis, endocarditis). Other causes of anemia of chronic disease are as follows:
- Chronic inflammation (e.g., connective tissue disorders, burns)
- Malignant disease (e.g., carcinomas, lymphomas)
- Endocrine disorders (e.g., hypothyroidism, hypogonadism, hypopituitarism)
- Chronic renal disease
- Chronic liver disease
- IBD

**Treatment**
- Rx is aimed at identification and Rx of underlying disease.
- Erythropoietic agents (epoetin alfa, epoetin beta, and darbepoetin) can be used in pts w/chronic kidney disease, in HIV pts undergoing myelosuppressive Rx, and in pts w/cancer who are undergoing chemotherapy.

### 38 ANEMIA, PERNICIOUS

**Definition**
Autoimmune disease resulting from Abs against intrinsic factor and gastric parietal cells.

**Diagnosis**
- H&P
  - The clinical presentation of pernicious anemia varies w/ the stage. Initially, pts may be asymptomatic. In advanced stages, pts may present w/ impaired memory, depression, gait disturbances, paresthesias, and complaints of generalized weakness.
  - Labs
    - CBC generally reveals macrocytic anemia and leukopenia w/ hypersegmented neutrophils.
    - MCV is generally significantly ↑ in the advanced stages.
    - Reticulocyte count is ↓/ml.
    - Falsely ↓ serum cobalamin levels can occur in pts w/severe folate deficiency, in pts using high doses of ascorbic acid, and when cobalamin levels are measured after nuclear medicine studies (radioactivity interferes w/cobalamin radioimmunoassay measurement).
Diseases

Chapter 3  Diseases and Disorders

- Falsely ↑/N levels in pts w/cobalamin deficiency can occur in severe liver disease or chronic granulocytic leukemia.
- Schilling test is abnl in part I; part II corrects to nl after administration of intrinsic factor.
- Labs used for detecting cobalamin deficiency in pts w/ nl vitamin B₁₂ levels include serum and urinary methylmalonic acid level (↑), total homocysteine level (↑), intrinsic factor Ab (+).
- ↑ Plasma methylmalonic acid (P-MMA) does not predict clinical manifestations of vitamin B₁₂ deficiency and should not be used as the only marker for diagnosis of B₁₂ deficiency.
- Additional laboratory abnormalities can include ↑ LDH, direct hyperbilirubinemia, and ↓ haptoglobin.
- Endoscopy and bx for atrophic gastritis may be performed in selected cases.

Etiology
- Gastric anti-parietal cell Abs in >70% of pts, anti–intrinsic factor Abs in >50% of pts
- Atrophic gastric mucosa

Treatment
- Traditional Rx of a cobalamin deficiency consists of IM injections of vitamin B₁₂ 1000 µg/wk for the initial 4-6 wk followed by 1000 µg/mo IM indefinitely. When hematologic parameters have returned to nl range, intranasal cyanocobalamin may be used in place of IM cyanocobalamin. The initial dose of intranasal cyanocobalamin is one spray (500 µg) in one nostril q wk. Monitor response and ↑ dose if serum B₁₂ levels decline. Consider return to IM vitamin B₁₂ supplementation if decline persists.
- Oral cobalamin (1000-2000 µg/day) is effective in mild cases of pernicious anemia because about 1% of an oral dose is absorbed by passive diffusion, a pathway that does not require intrinsic factor. Cost for 1 mo of oral Rx is approximately $5.

Clinical Pearls
- Dx is crucial because failure to treat may result in irreversible neurologic deficits.
- Avoid folic acid supplementation w/o proper vitamin B₁₂ supplementation.
- Absence of anemia or macrocytosis does not exclude the dx of cobalamin deficiency. Anemia is absent in 20% of pts w/cobalamin deficiency, and macrocytosis is absent in >30% of pts at the time of dx. It can be blocked by concurrent iron deficiency or anemia of chronic disease and may be masked by thalassemia trait.

**39 ANEMIA, SIDEROBLASTIC**

Definition
Blood disorder resulting from defective heme synthesis, classified as hereditary, acquired, and reversible. Sideroblastic anemia can be thought of as an iron-loading anemia secondary to defective heme synthesis.

Diagnosis

**Labs**
- Hypochromic anemia (↓ MCV, ↑ RDW)
- Peripheral smear: dimorphic large and small cells revealing “Pappenheimer bodies” or siderocytes when stained for iron
- Bone marrow: ringed sideroblasts, which represent iron storage in the mitochondria of normoblasts

Etiology
- Primary hereditary sideroblastic anemia may be inherited as a sex-linked recessive disease.
- Secondary acquired sideroblastic anemia can be caused by alcohol, isoniazid, pyrazinamide, cycloserine, chloramphenicol, and copper deficiency.
- Lead poisoning
**Chapter 3  Diseases and Disorders**

**Treatment**
- Avoid alcohol
- Sideroblastic anemia secondary to isoniazid, pyrazinamide, and cycloserine: vitamin B\(_6\) (50-200 mg/day)
- Vitamin B\(_6\) (50-200 mg/day) will result in significant response in 35% of hereditary sideroblastic anemias; the remainder will require periodic blood transfusions when symptomatic
- Erythropoietin injections: useful in primary acquired sideroblastic anemia

**Clinical Pearl**
- Organ dysfunction resulting from iron overload will require periodic phlebotomies (indicated when serum iron levels >500 µg/L) and use of deferoxamine in pts requiring frequent blood transfusions.

### 40 ANEURYSM, ABDOMINAL AORTA

**Definition**
Permanent localized dilation of the abd aortic artery of at least 50% compared w/the nl diameter (2.3 cm in men, 1.9 cm in women).

**Diagnosis**

**Imaging**
- Abd U/S: preferred initial imaging modality; estimates size within 0.4 cm; not very good in estimating proximal extension to renal arteries or involvement of iliac arteries
- CT scan and angiography: more accurate, used preoperatively

**Etiology**
- Atherosclerotic (degenerative or nonspecific): risk factors are older age, smoking, male sex, white race, FHx AAA, occlusive atherosclerotic disease
- Genetic (e.g., Ehlers-Danlos syndrome)
- Trauma
- Cystic medial necrosis (Marfan syndrome)
- Arteritis, inflammatory
- Mycotic, syphilitic

**Treatment**
- Monitoring by U/S or CT q 6-12 mo for AA measuring 4-5.4 cm. In pts w/AAA <4.0 cm, monitoring q 2 yr is reasonable. Vascular surgical referral should be made in asymptomatic pts w/AAA 4.0 cm or greater or in rapidly expanding aneurysms of 0.6-0.8 cm/yr, especially if sx are present.
- Surgical repair for infrarenal or juxtarenal AAA ≥5.5 cm

**Clinical Pearls**
- Mortality rate for elective repair of nonruptured aneurysms is 4%.
- Mortality after rupture is >80%.
- Almost 75% of AAAs are asymptomatic and are discovered on routine examinations (pulsatile epigastric mass) or serendipitously when studies are ordered for other complaints.
- U/S of AA to screen for AAA should be considered in all male smokers >65 years old.

### 41 ANGIOEDEMA

**Definition**
Cutaneous swelling caused by the release of vasoactive mediators is called urticaria and angioedema. Urticaria causes edema of the superficial dermis. Angioedema involves the deep layers of the dermis and the SC tissue.

**Diagnosis**

**H&P**
- Angioedema is characterized by the following: nonpruritic, burning, not well demarcated; involves eyelids, lips, tongue, and extremities and resolves slowly. It can involve the larynx, causing respiratory distress.
Diseases and RF, are now disorders including overlapping of spondylitis of the group one for rheumatoid a commonly associated condition. It is characterized by inflammatory factors (e.g., cold, physical exercise, pressure, and vibration), medications (ACEIs), and connective tissue diseases.

Etiology
- Acquired (allergic or idiopathic) usually associated with other diseases, most commonly B-cell lymphoproliferative disorders, but may also result from formation of auto-Abs directed against C1 inhibitor protein. Other causes of angioedema include infections (e.g., HSV, hepatitis B, coxsackieviruses A and B, Streptococcus, Candida, Ascaris, and Strongyloides), insect bites and stings, physical factors (e.g., sun, cold, physical exercise, pressure, and vibration), and connective tissue diseases.
- Hereditary: autosomal dominant caused by a deficiency of C1 esterase inhibitor (C1-INH)

Treatment
- Acute life-threatening angioedema involving the larynx:
  - SC epinephrine 0.3 mg in solution of 1:1000
  - Diphenhydramine 50 mg IV or IM
  - Cimetidine 300 mg IV or ranitidine 50 mg IV or IM
  - Methylprednisolone 125 mg IV
- Mainstay Rx in angioedema is H1 antihistamines (e.g., hydroxyzine, loratadine, fexofenadine).
- H2 receptor antagonist (e.g., ranitidine, cimetidine) can be added in severe cases.
- Corticosteroids tapered during several days (e.g., prednisone 60 mg on day 1, ↓ by 5 mg qd until finished) and the tricyclic antidepressant doxepin (25-50 mg qd) are useful in chronic resistant cases.

Clinical Pearls
- Antihistamines achieve symptomatic relief in >80% of pts.
- Chronic angioedema can last for months and even years.

ANKYLOSING SPONDYLITIS
Definition
Chronic inflammatory condition involving the sacroiliac joints and axial skeleton characterized by ankylosis and enthesitis (inflammation at tendon insertions). It is one of a group of several overlapping syndromes, including spondylitis associated with Reiter’s syndrome, psoriasis, and IBD. Pts are typically seronegative for the RF, and these disorders are now commonly called rheumatoid variants or seronegative spondyloarthopathies.

Diagnosis
H&P
The modified New York criteria are often used for diagnosis:
- Low back pain of >3 mo duration, improved by exercise and not relieved by rest
- Morning stiffness lasting >30 min
- Limitation of lumbar spine movement in sagittal and frontal planes
- ↓ Chest expansion below nl values for age and sex
- Bilateral sacroiliitis of moderate grade or greater

Labs
- ↑ ESR, CRP, (-) ANA and RF, (+) HLA-B27 antigen in >90% of pts

Imaging
- Back x-rays: vertebral bodies may become demineralized, and a typical "squaring off" occurs. With progression, calcification of the annulus fibrosus and paravertebral ligaments develops, giving rise to the so-called bamboo spine appearance. End result may be a forward protruding cervical spine and a fixed dorsal kyphosis.
- MRI may be helpful in detecting early inflammatory lesions and is especially helpful when the hx is suggestive but plain films are nl.

Etiology
- Unknown. Genetic factors may play a role.
Treatment
- Exercises primarily to maintain flexibility; general aerobic activity also important
- Postural training: pts must be instructed to sit in the erect position and to avoid stooping. Sleeping should be in the supine position on a firm mattress; pillows should not be placed under the head or knees.
- NSAIDs for pain control
- Use of DMARDs, such as tumor necrosis factor antagonists like etanercept, appears promising.

Clinical Pearl
- Years may pass between the onset of sx and ultimate diagnosis because of the frequency of nonspecific low back pain from other disorders.

43 ANOREXIA NERVOSA

Definition
Psychiatric disorder characterized by abnl eating behavior, severe self-induced weight loss, and a specific psychopathology.

Diagnosis
H&P
- A dx can be made by the following DSM-IV diagnostic criteria for anorexia nervosa:
  - Refusal to maintain BW at or above a minimally nl weight for age and height (e.g., weight loss leading to maintenance of BW <85% of that expected or failure to make expected weight gain during a period of growth, leading to BW <85% of that expected)
  - Intense fear of gaining weight or becoming fat, even though underweight
  - Disturbance in the way in which BW or shape is experienced, undue influence of BW or shape on self-evaluation, or denial of the seriousness of the current low BW
  - In postmenarchal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles (a woman is considered to have amenorrhea if her periods occur only after hormone, e.g., estrogen, administration)
- There are two major types of anorexia nervosa:
  - Restricting type: during the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).
  - Binge-eating/purging type: during the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).
- The SCOFF questionnaire is a useful screening tool used in England for eating disorders. It consists of the following five questions:
  - Do you make yourself Sick because you feel full?
  - Have you lost Control over how much you eat?
  - Have you lost more than One stone (about 6 kg) recently?
  - Do you believe yourself to be Fat when others say you are thin?
  - Does Food dominate your life?
- A + response to ≥2 questions has a reported sensitivity of 100% for anorexia and bulimia and an overall specificity of 87.5%.

Labs
- Leukopenia, thrombocytopenia, anemia, ↓ ESR, ↓ complement levels, ↓ CD4 and CD8 cells may be present.
- Metabolic alkalosis, hypocalcemia, hypokalemia, hypomagnesemia, hypercholesterolemia, and hypophosphatemia may be present.
- ↑ Plasma carotene levels are useful to distinguish these pts from others on starvation diets.

Imaging
- Baseline ECG should be performed on all pts w/anorexia nervosa. Routine monitoring of pts w/↑ QT interval is necessary; sudden death in these pts is often caused by ventricular arrhythmias related to QT interval prolongation.
**Etiology**
- Etiology unknown, but probably multifactorial (sociocultural, psychological, familial, and genetic factors).
- H/o sexual abuse reported in nearly 50% of pts w/anorexia nervosa.
- Psychological factors: anorexics often have an incompletely developed personal identity. They struggle to maintain a sense of control over their environment, they usually have a low self-esteem, and they lack the sense that they are valued and loved for themselves.

**Treatment**
- A multidisciplinary approach w/psychological, medical, and nutritional support is necessary.
- A goal weight should be set and the pt should be initially monitored at least once a wk in the office setting. The target weight is 100% of ideal BW for teenagers and 90%-100% for older pts.
- Weight gain should be gradual (1-3 lb/wk) to prevent gastric dilation.
- Electrolyte levels should be strictly monitored.
- Mealtime should be a time for social interaction, not confrontation.
- Postprandially, sedentary activities are recommended. The pt’s access to a bathroom should be monitored to prevent purging.
- Pharmacologic treatment generally has no role in anorexia nervosa unless major depression or another psychiatric disorder is present. SSRIs can be used to alleviate the depressed mood and moderate obsessive-compulsive behavior in some individuals.

**Clinical Pearls**
- The long-term prognosis is generally poor and marked by recurrent exacerbations. The percentage of pts w/anorexia nervosa who fully recover is modest. Most pts continue to suffer from a distorted body image, disordered eating habits, and psychic difficulties.
- Most pts w/anorexia nervosa will recover menses within 6 mo of reaching 90% of their ideal BW. Pts w/anorexia nervosa can become pregnant despite amenorrhea.
- Mortality rates vary from 5%-20%. Frequent causes of death are electrolyte abnormalities, starvation, and suicide.
- ↑ QT interval is a marker for risk of sudden death.

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**44 ANOXIC BRAIN INJURY**

**Diagnosis**

**H&P**
- Global hypoxia from any cause can produce *posthypoxic action myoclonus (PHAM)*.
- Other manifestations may include cerebellar dysfunction, spasticity, dementia, cortical blindness.
- Postanoxic encephalopathy: irritability, confusion, apathy, agitation, mania, spasticity, incontinence, parkinsonism

**EEG**
- Generalized sharp waves, spikes, w/slow waves

**Etiology**
- MI
- Drug OD
- Airway obstruction
- Anesthesiology mishaps
- Near-drowning

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**45 ANTICOAGULANT THERAPY OVERDOSE (ANTICOAGULANT REVERSAL, REVERSAL OF ELEVATED INR)**

**Treatment**
- Stop warfarin. Warfarin inhibits the hepatic synthesis of vitamin K–dependent factors (II, VII, IX, X).
- Prothrombin complex concentrates (PCC) or FFP can be used in emergent situations. PPC are preferred first line, especially if volume overload is a concern.
In pts w/active bleeding or requiring invasive procedures, the administration of vitamin K should be preceded by the infusion of FFP (2-3 units [400-600 mL]). With significant PT prolongation and severe bleeding, up to 15 mL/kg may be needed. Measurement of PT and APTT should be obtained after the initial FFP infusion to determine need for additional infusions.

Vitamin K, 100-150 mg. PT (INR) begins to normalize after 12 hr and should normalize completely in 48 hr. Vitamin K can also be given SC (poorly absorbed in edematous pts), and IV (risk of anaphylaxis).

Partial reversal of coagulation with vitamin K for elective procedures:
- INR 3-6: vitamin K 1 mg PO
- INR 6-8: vitamin K 2.5 mg PO
- INR 8-12: vitamin K 5 mg PO

## 46 ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)

### Definition

Syndrome characterized by arterial or venous thrombosis or pregnancy loss and the presence of antiphospholipid Abs (APL). APL are Abs directed against either phospholipids or proteins bound to anionic phospholipids. Four types of APL have been characterized:
- False-positive serologic test results for syphilis
- Lupus anticoagulants
- Anticardiolipin (ACls)
- Anti-β₂-glycoprotein 1 Abs

The syndrome is referred to as primary APS when it occurs alone and as secondary APS in association w/SLE, other rheumatic disorders, or certain infections or medications. APS can affect all organ systems and includes venous and arterial thrombosis, recurrent fetal losses, and thrombocytopenia.

### Diagnosis

Diagnostic criteria of APS include at least one of the following clinical criteria and at least one of the following laboratory criteria:

**Clinical**
- Venous, arterial, or small-vessel thrombosis or
- Morbidity w/pregnancy (fetal death at >10 wk gestation; or premature births before 34 wk gestation secondary to eclampsia, preeclampsia, or severe placental insufficiency; or three or more unexplained consecutive spontaneous abortions <10 wk gestation)

**Labs**
- IgG or IgM ACL in medium or high titers or
- Lupus anticoagulant activity found on ≥2 occasions, at least 6 wk apart

### Etiology

Unclear. A binding protein (β₂-glycoprotein 1) may be the key immunogen in the APS.

Some APS + families exist, and HLA studies have suggested associations w/HLA DR7, DR4, and Dw7 plus Drw53.

### Treatment

For + APL and venous thrombosis: initial anticoagulation w/heparin, then lifelong warfarin treatment, INR 2.0-3.0

For + APL w/arterial thrombosis:
- Cerebral arterial thrombosis: ASA 325 mg qd or warfarin Rx (INR 1.4-2.8)
- Noncerebral arterial thrombosis: warfarin Rx (INR 2.0-3.0)

For pregnant women w/previously diagnosed APS:
- Warfarin should be discontinued secondary to its teratogenic effects.
- ASA, 81 mg, and heparin SC to PTT of 1.5-2× control value.
- IVIG and prednisone have also been used w/success if ASA and heparin fail.

For pregnant women w/+ APL Abs and a h/o <3 spontaneous abortions:
- ASA 81 mg qd at conception and SC heparin 5,000-10,000 IU q12h at time of documented viable intrauterine pregnancy (approximately 7 wk gestation) until 6 wk post partum.
Aortic dissection occurs when an intimal tear allows blood to dissect between medial layers of the aorta. Two main classification schemes based on the location of dissection are (Fig. 3-12)

- DeBakey: type I, ascending and descending aorta; II, ascending aorta; III, descending aorta
- Stanford: type A, ascending aorta (proximal); type B, descending aorta (distal)

**Clinical Pearls**
- 1%-5% of healthy subjects have anticardiolipin and lupus anticoagulant Abs.
- 12%-30% of pts w/SLE have ACLs, and 15%-34% have lupus anticoagulant Abs.
- APS pts have a 20%-70% risk for recurrent thrombosis.
- Initial arterial thrombosis tends to be followed by arterial events, and initial venous thrombosis tends to be followed by venous events.
- Catastrophic APS is associated w/a high mortality rate, approaching 50%.
- Incidence for development of catastrophic APS is approximately 0.8% among APS pts.

**47 AORTIC DISSECTION**

**Definition**
Aortic dissection occurs when an intimal tear allows blood to dissect between medial layers of the aorta.
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Diagnosis
H&P
- Clinical presentation: sudden onset of severe chest pain often described as sharp, tearing, or ripping. Pain can be anterior w/ascending aortic dissection or back pain w/descending aortic dissection.
- Pulse and BP differentials common (38%), caused by partial compression of subclavian arteries.
- Most pts present w/severe HTN. Hypotension (25%) can indicate bleeding, cardiac tamponade, or severe aortic regurgitation.

Imaging
- TEE: study of choice in unstable pts. Sensitivity is 97%-100%.
- MRI: gold standard and gives best information to surgeons. Sensitivity is 90%-100% but length of test and difficult access not suitable for stable intubated pts.
- CXR: may show widened mediastinum (62%).

Etiology
- Intimal degeneration of aorta
- Risk factors include HTN, atherosclerosis, FHx of aortic aneurysms, trauma, collagen disorders, bicuspid aortic valve, aortic coarctation, vasculitis, Turner’s syndrome, cocaine abuse

Treatment
- Admit to ICU
- Target SBP 100-120, HR <60 bpm to ↓ aortic wall stress
- IV β-blockers are cornerstones of treatment.
- Propranolol 1 mg q3-5min, metoprolol 5 mg IV q5min, or labetalol 20 mg IV, then 20-80 mg q10min, followed by IV nitroprusside 0.3-10 mg/kg/min
- Nitroprusside should not be used w/o β-blockade because vasodilation can induce reflex sympathetic stimulation and ↑ aortic sheer stress.
- IV CCBs w/negative inotropy may be used.
- Pain control: morphine
- Proximal dissections: emergent surgery to prevent rupture or pericardial effusion
- Distal dissections: treated medically unless distal organ involvement or impending rupture occurs
- Evolving role for endovascular stent placement as less invasive treatment of high-risk surgical pts

Clinical Pearls
- 85% mortality within 2 wk if untreated
- Proximal dissection is a surgical emergency. Time is critical; mortality is 1%-3% per hr.
- Overall, in-hospital mortality is 30% w/proximal dissections and 10% w/distal dissections.
- After surgical repair, pts should be observed w/frequent MRI because recurrent aneurysm or dissection is common in first 2 yr.

48 AORTIC REGURGITATION
(AORTIC INSUFFICIENCY, AI)

Definition
Retrograde blood flow into the LV from the aorta secondary to incompetent aortic valve.

Diagnosis
H&P
- The clinical presentation varies according to whether AI is acute or chronic.
  - Chronic AI is well tolerated (except when secondary to infective endocarditis), and the pts remain asymptomatic for years. Common manifestations after significant deterioration of left ventricular function are dyspnea on exertion, syncope, chest pain, and CHF.
  - Acute AI manifests primarily w/hypotension due to a sudden fall in CO. A rapid rise in left ventricular diastolic pressure results in a further ↓ in coronary blood flow.
Physical findings in chronic AI include the following:
- Widened pulse pressure (markedly ↑ SBP, ↓ DBP)
- Bounding pulses, head “bobbing” w/each systole (de Musset’s sign) are present; “water-hammer” or collapsing pulse (Corrigan’s pulse) can be palpated at the wrist or on the femoral arteries (“pistol shot” femorals) and is caused by rapid rise and sudden collapse of the arterial pressure during late systole; capillary pulsations (Quincke’s pulse) may occur at the base of the nail beds.
- A to-and-fro double Duroziez murmur may be heard over femoral arteries w/slight compression.
- Popliteal systolic pressure is ↑ over brachial systolic pressure ≥40 mm Hg (Hill’s sign).

Cardiac auscultation:
- Displacement of cardiac impulse downward and to the pt’s left
- S₃ heard over the apex
- Decrescendo, blowing diastolic murmur heard along LSB
- Low-pitched apical diastolic rumble (Austin-Flint murmur) caused by contrast of the aortic regurgitant jet w/the left ventricular wall
- Early systolic apical ejection murmur
- In pts w/acute AI, both the wide pulse pressure and the large SV are absent. A short blowing diastolic murmur may be the only finding on PE.

Imaging
- Echo: coarse diastolic fluttering of the anterior mitral leaflet; LVH in pts w/chronic AI
- Cardiac catheterization: assesses degree of left ventricular dysfunction, confirms the presence of a wide pulse pressure, assesses surgical risk, and determines if there is coexistent CAD
- CXR:
  - LVH (chronic AI)
  - Aortic dilatation
  - NL cardiac silhouette w/pulmonary edema: possible in pts w/acute AI
- ECG: LVH

Etiology
- Infective endocarditis
- Rheumatic fibrosis
- Trauma w/valvular rupture
- Congenital bicuspid aortic valve
- Myxomatous degeneration
- Syphilitic aortitis
- Rheumatic spondylitis
- SLE
- Aortic dissection
- Fenfluramine, dexfenfluramine
- Takayasu’s arteritis, granulomatous arteritis

Treatment
Medical
- Digitalis, diuretics, ACEIs, and sodium restriction for CHF; nitroprusside in pts w/acute AI
- Long-term vasodilator Rx w/ACEIs or nifedipine for reducing or delaying the need for aortic valve replacement in asymptomatic pts w/severe aortic regurgitation and nl left ventricular function

Surgical
Reserved for:
- Symptomatic pts w/chronic AI despite optimal medical Rx
- Pts w/acute AI (i.e., infective endocarditis) producing LVH
- Evidence of systolic failure:
  - Echo: fractional shortening <25%
  - Echocardiographic and diastolic dimension >55 mm
  - Angiographic EF <50% or end-systolic volume index (ESVI) >60 mL/m²
Evidence of diastolic failure:
• Pulmonary pressure >45 mm Hg systolic
• LVEDP >15 mm Hg at catheterization
• Pulmonary HTN detected on examination
• “55 rule” used to determine the timing of surgery: surgery should be performed before EF < 55% or end-systolic dimension >55 mm.

Clinical Pearl
• Prognosis depends on underlying condition and left ventricular function; AI (except when secondary to infective endocarditis) is generally well tolerated, and pts remain asymptomatic for years.

Aortic Stenosis (AS)

Definition
Obstruction to systolic left ventricular outflow across the aortic valve.

Diagnosis

H&P
• Rough, loud systolic diamond-shaped murmur, best heard at base of heart and transmitted into neck vessels; often associated w/ a thrill or ejection click; may also be heard well at the apex
• Absence or ↓ intensity of sound of aortic valve closure (in severe AS)
• Late, slow-rising carotid upstroke w/↓ amplitude
• Strong apical pulse
• Narrowing of pulse pressure in later stages of AS
• Medical hx should focus on sx and potential complications: angina, syncope (particularly w/exertion), CHF, GI bleeding (in pts w/associated hemorrhagic telangiectasia [AVM])

Imaging
• Echo: thickening of LV wall; if the pt has valvular calcifications, multiple echoes may be seen from within the aortic root, and there is poor separation of the aortic cusps during systole. Gradient across the valve can be estimated but is less precise than w/cardiac cath.
• ECG:
  • LVH (found in >80% of pts)
  • ST-T wave changes
  • AF: frequent

Etiology
• Rheumatic inflammation of aortic valve
• Progressive stenosis of congenital bicuspid valve (found in 1%-2% of population)
• Idiopathic calcification of the aortic valve
• Congenital (major cause of AS in pts <30 yr)

Treatment

Medical
• Diuretics and sodium restriction if CHF is present. ACEIs are relatively contraindicated.
• CCB verapamil: useful to control rate of AF if present.

Surgical
• Valve replacement in symptomatic pts. The presence of moderate or severe valvular calcification, together w/ a rapid ↑ in aortic jet velocity and ↑ BNP, identifies pts w/ a very poor prognosis who should be considered for early valve replacement rather than have surgery delayed until sx develop.
• Surgical mortality rate for valve replacement is 3%-5%; however, it varies w/ pt’s age (>8% in pts >75 yr old).
• Balloon valvuloplasty: useful in infants and children or poor surgical candidates who do not have calcified valve apparatus; it can be done as an intermediate procedure to stabilize high-risk pts before surgery.

Clinical Pearls
• Sx appear when the valve orifice ↓ to <1 cm² (nl orifice is 3 cm²).
• The stenosis is considered severe when the orifice is <0.5 cm²/m² or the pressure gradient is 50 mm Hg or higher.
50 APPENDICITIS

Definition
Acute inflammation of the appendix.

Diagnosis
H&P

- Abd pain: initially the pain may be epigastric or periumbilical in nearly 50% of pts; it subsequently localizes to the RLQ within 12-18 hr. Pain can be found in back or right flank if appendix is retrocecal or in other Abd locations if there is malrotation of the appendix.

- Pain w/right thigh extension (psoas sign), low-grade fever: temperature may be >38°C if there is appendiceal perforation.

- Pain w/internal rotation of the flexed right thigh (obturator sign) is present.

- RLQ pain on palpation of the LLQ (Rovsing’s sign): PE may reveal right-sided tenderness in pts w/pelvic appendix.

- Point of maximum tenderness is in the RLQ (McBurney’s point).

- N/V, tachycardia, cutaneous hyperesthesias at the level of T12 can be present.

Labs

- CBC w/diff: leukocytosis w/a left shift (>90% of pts). Total WBC count is generally <20,000/mm³. Higher counts may be indicative of perforation. A ↓ Hgb and Hct in an older pt should raise suspicion for carcinoma of the cecum.

- Microscopic hematuria and pyuria may occur in <20% of pts.

Imaging

- CT abd/pelvis (sensitivity >90%, accuracy >94%). A distended appendix, periappendiceal inflammation, and thickened appendiceal wall are indicative of appendicitis.

- U/S (sensitivity 75%-90%): useful in younger women and pregnant women when dx is unclear. NI U/S findings should not deter surgery if the H&P are indicative of appendicitis.

Etiology
Obstruction of the appendiceal lumen w/subsequent vascular congestion, inflammation, and edema; common causes of obstruction are

- Fecaliths: 30%-35% of cases (most common in adults)

- Foreign body: 4% (fruit seeds, pinworms, tapeworms, roundworms, calculi)

- Inflammation: 50%-60% of cases [submucosal lymphoid hyperplasia [most common etiology in children, teens]]

- Neoplasms: 1% (carcinoids, metastatic disease, carcinoma)

Treatment

- Urgent appendectomy (laparoscopic or open), correction of fluid and electrolyte imbalance w/vigorous IV hydration and electrolyte replacement

- IV abx prophylaxis to cover gram-negative bacilli and anaerobes (ampicillin-sulbactam 3 g IV q6h or piperacillin-tazobactam 4.5 g IV q8h in adults)

Clinical Pearl

- Perforation is common (20% in adult pts). Indicators of perforation are pain lasting >24 hr, leukocytosis >20,000/mm³, temp >102°F, palpable abd mass, and peritoneal findings.

51 ARTHRITIS, INFECTIOUS (SEPTIC ARTHRITIS)

Definition
Joint disease most often caused by hematogenous spread of organisms from a distant site of infection. Direct penetration of the joint as a result of trauma or surgery and spread from adjacent osteomyelitis may also cause bacterial arthritis. Any joint in the body may be affected. Gonococcal arthritis causes a distinct clinical syndrome and is often considered separately.

Diagnosis
H&P

- Acute onset of a swollen painful joint, fever

- Limited range of motion of joint, erythema, ↑ warmth around the joint
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Labs
- Joint aspiration, Gram stain and C&S of synovial fluid, blood cultures, CBC w/diff, ESR, and culture of possible extra-articular source of infection
- Synovial fluid leukocyte count is usually ↑ (>50,000 cells/mL) w/a diff count of 80% or more polymorphonuclear cells.

Imaging
- X-ray of affected joint
- CT scan: useful for early dx of infections of the spine, hips, and sternoclavicular and sacroiliac joints
- Technetium and gallium scans: + but do not allow differentiation of infection from inflammation. Indium-labeled WBC scans are less sensitive but more specific.

Etiology
- Bacteria spread from another locus of infection
- Most common nongonococcal organisms are S. aureus, beta-hemolytic strep, and gram-negative bacilli

Treatment
- IV abx immediately after joint aspiration and Gram stain of synovial fluid
- Gram-positive cocci: nafcillin 2 g IV q4h. If clinical suspicion of MRSA, use vancomycin 1 g IV q12h
- Gram-negative bacilli: third-generation ceph or antipseudomonal PCN plus AG
- Suspected gonococcal infection: ceftriaxone 1 g IV q24h

Clinical Pearls
- Predisposing factors for infectious arthritis are RA, prosthetic joints, advanced age, immunodeficiency.
- Most commonly affected joint in adult: knee and hip; in children: hip.
- In gonococcal infection, typical pattern is a migratory polyarthritis or tenosynovitis and presence of small pustules on the trunk or extremities.

52 ARTHRITIS, JUVENILE RHEUMATOID (JRA, JUVENILE IDIOPATHIC ARTHRITIS)

Definition
Arthritis beginning before 16 yr of age.

Diagnosis
H&P
Clinical presentation is usually one of 3 types:
- Systemic or acute febrile JRA (20% of cases)
  - Characterized by extra-articular manifestations, especially spiking fevers and a typical rash that frequently appears in the evening and may be elicited by gently scratching the skin in susceptible areas (Koebner’s phenomenon)
  - Possible splenomegaly, generalized lymphadenopathy, pericarditis, and myocarditis
  - Often, min. articular findings overshadowed by systemic sx
- Pauciarticular or oligoarticular JRA (50% of cases)
  - Involves <5 joints
  - Usually involves the larger joints, such as the knees, elbows, and ankles
  - Systemic features are often minimal.
  - Chronic iridocyclitis develops in nearly 30% of cases.
  - Accelerated growth of the affected limb from chronic hyperemia, possibly resulting in a temporary leg length discrepancy
- Polyarticular JRA (30% of cases)
  - Involves ≥5 joints
  - Resembles the adult disease in its symmetric involvement of the small joints of the hands and feet
  - Cervical spine involvement common and may produce marked loss of motion
  - Early closure of ossification centers of the mandible, often producing a marked receding chin
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ARTHRITIS, PSORIATIC

Definition
Inflammatory spondyloarthritis occurring in pts w/psoriasis who are usually seronegative for RF. It is often included in a class of disorders called *rheumatoid variants* or *seronegative spondyloarthropathies*.

Diagnosis

H&P
- Gradual clinical onset w/asymmetric involvement of scattered joints, skin psoriasis
- Symmetric arthritis similar to RA occurs in 15% of pts; sacroiliitis may occur in a small number of cases.
- Selective involvement of DIP joints (described in “classic cases”) occurs in only 5% of pts; when present is often accompanied by dystrophic changes in the nails (pitting, ridging).

Labs
- Slight ↑ ESR, mild anemia; + HLA-B27 antigen often found in pts w/sacroiliitis

Imaging
- Peripheral joint findings similar to RA but erosive changes in the distal phalangeal tufts characteristic of psoriatic arthritis
- Bony osteolysis, periostral new bone formation, sacroiliitis, development of vertebral syndesmophytes (osteophytes)
- Characteristic “pencil-in-cup” appearance on x-ray w/erosion of proximal and distal phalanges

Etiology
- Unknown

Treatment
- NSAIDs for pain control
- Splinting, joint protection, physical Rx
- Occasional intra-articular steroid injections
- DMARDs rarely required

Clinical Pearl
- Early dx may be difficult to establish because the arthritis may develop before skin lesions appear.

ASBESTOSIS

Definition
Slowly progressive diffuse interstitial fibrosis resulting from dose-related inhalation exposure to fibers of asbestos.
**Diagnosis**

**H&P**
- Insidious onset of SOB w/exertion is usually the first sign of asbestosis.
- Dyspnea becomes more severe as the disease advances; w/time, progressively less exertion is tolerated.
- Cough is frequent and usually paroxysmal, dry, and nonproductive.
- Scant mucoid sputum may accompany the cough in the later stages of the disease.
- Fine end-respiratory crackles (rales, crepitations) are heard more predominantly in the lung bases.
- Digital clubbing, edema, JVD may be present.

**Labs**
- PFTs: ↓ VC, ↓ TLC
- ABGs: hypoxemia, hypercarbia in advanced stages

**Imaging**
- CXR: small, irregular shadows in lower lung zones; thickened pleura, calcified plaques (present under diaphragms and lateral chest wall)
- CT of chest confirms the dx.

**Etiology**
- Inhalation of asbestos fibers

**Treatment**
- Prompt identification and treatment of respiratory infections
- Supplemental oxygen on a PRN basis
- Annual influenza vaccination, pneumococcal vaccination every 5 years

**Clinical Pearls**
- Pts w/asbestosis have ↑ risk for mesotheliomas, lung cancer, and TB; recent reports indicate that the risk of asbestos-induced lung cancer may be overestimated.
- Smokers w/asbestos exposure have a 3× ↑ risk of bronchogenic carcinoma.

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**ASCARIASIS**

**Definition**
Parasitic infection caused by the nematode *Ascaris lumbricoides*.

**Diagnosis**

**H&P**
- The majority of those infected are asymptomatic; however, clinical disease may arise from pulmonary hypersensitivity, intestinal obstruction, and secondary complications.
- Clinical presentation: occurs 9-12 days after ingestion of eggs and corresponds to larva migration through the lungs. Nonproductive cough, fever, substernal chest discomfort may be present. Migration of worms in biliary tree may mimic biliary colic or pancreatitis.
- Expectoration or fecal passage of adult worm

**Labs**
- Examination of stool for *Ascaris* ova
- Eosinophilia: most prominent early in infection and subsides as adult worm infestation is established in intestines
- Anti-*Ascaris* IgG4 blood level by ELISA is a sensitive and specific marker of infection

**Imaging**
- CXR may reveal bilateral oval or round infiltrates (*Loeffler’s syndrome*).
- Plain films of abd and contrast studies may reveal worm masses in loops of bowel.

**Etiology**
- Infestation by the nematode *Ascaris lumbricoides*

**Treatment**
- Mebendazole 100 mg tid for 3 days
- Albendazole 400 mg PO as single dose is also effective.
- In pregnant pts, use pyrantel pamoate.
- Piperazine citrate is used in cases of intestinal or biliary obstruction.
**Clinical Pearls**
- Transmission is usually hand to mouth, but eggs may be ingested through transported vegetables grown in contaminated soil.
- Within human host, adult worm life span is 1-2 yr.

**56 ASCITES**

**Definition**
Accumulation of excess fluid in the peritoneal cavity, most commonly caused by liver cirrhosis.

**Diagnosis** *(Fig. 3-13)*

**H&P**
- Hx viral hepatitis, alcoholism, ↑ abd girth, ↑ LE edema, IV drug abuse, + sexual hx (e.g., men who have sex w/men), blood transfusions
- Bulging flanks, flank dullness on percussion, fluid wave on abd examination, LE edema, shifting dullness on abd examination
- Physical signs associated w/cirrhosis: spider angiomas, jaundice, loss of body hair, muscle wasting, bruising, gynecomastia, testicular atrophy, hemorrhoids, caput medusae

![Diagram of diagnostic algorithm for ascites](image)

**FIGURE 3-13.** Diagnostic algorithm for ascites.

**Labs**
- Diagnostic paracentesis: lab tests on fluid should include CBC w/diff, alb, total protein, Gram stain. Optional tests include LDH, amylase, glucose level, AFB. A serum/ascites alb gradient (SAAG) should be calculated in all pts. If the SAAG is >1.1, the cause of ascites can be attributed to portal HTN. If SAAG is <1.1, a non–portal HTN cause of ascites must be sought.
- Serum ALT, AST, total and direct bili, alb, alk phos, GGTP, hepatitis screen, CBC, INR, lytes, BUN, Cr
- Liver bx in selected pts (e.g., those w portal HTN of uncertain etiology)
Imaging
- Abd U/S is the most sensitive measure of detecting ascitic fluid; CT is a viable alternative.
- EGD to evaluate for esophageal varices if ascites is secondary to portal HTN

Etiology
- Ascites is the most common complication of cirrhosis (75% of cases). It occurs in 50% of individuals w/cirrhosis within 10 yr of dx. Other causes are malignant disease (10%), pancreatitis (5%), cardiac failure (3%), and TB (3%).

Treatment
- Sodium-restricted diet (max 60-90 mEq/day)
- Fluid restriction to 1 L/day in pts w/hyponatremia
- Pts w/moderate-volume ascites causing only moderate discomfort may be treated w/spironolactone 50-200 mg/day or amiloride 5-10 mg/day. Add furosemide 20-40 mg/day in the first several days of treatment, monitoring renal function carefully for signs of prerenal azotemia. In pts w/o edema, goal weight loss is 300-500 g/day; in pts w/edema, it is 800-1000 g/day.
- Pts w/large-volume ascites causing marked discomfort can be treated with:
  - Large-volume paracentesis w/infusion of alb
  - Diuretic Rx until significant loss of fluid is noted (max spironolactone 400 mg qd and furosemide 160 mg/day). There is no difference in long-term mortality rate; however paracentesis is faster, more effective, and associated w/fewer adverse effects.
  - Placement of TIPS

Clinical Pearl
- Presence of SBP in pts w/ascites is 10%-30%.

57 ASEPTIC NECROSIS
Definition
Disorder characterized by cell death in components of bone.

Diagnosis
H&P
- May be asymptomatic; pain in the involved area exacerbated by movement or weight bearing is usually present.

Imaging
- MRI is most sensitive imaging test.
- Bone scan: early findings “cold” area, later ↑ radionuclide uptake.
- CT scan: may reveal central necrosis and area of collapse.
- Plain x-rays: earliest changes include diffuse osteopenia, areas of radiolucency w/sclerotic border, and linear sclerosis. Later, a subchondral lucency (crescent sign) indicates subchondral fx. More advanced cases reveal flattening, collapsed bone, and abnl bone contour. In late disease, osteoarthritic changes are seen.

Etiology
- Impairment of blood supply to the involved bone

Treatment
- ↓ Weight bearing of affected area
- Core decompression: effectiveness 35%-95% in early phases
- Bone grafting
- Osteotomies
- Joint replacement

Clinical Pearls
- Contralateral joint involvement is common (30%-70%).
- Commonly seen in nonunion fx of the scaphoid and in femoral neck fx.

58 ASPERGILLOSIS
Definition
Several forms of a broad range of illnesses caused by an infection w/the Aspergillus species.
Diagnosis

H&P
- Clinical presentation: variable, but most pts present w/cough, fever, dyspnea, hemoptysis.

Invasive Aspergillosis
- Definitive dx requires demonstration of tissue invasion as seen on a bx specimen or a positive culture from the tissue obtained by an invasive procedure such as transbronchial bx.
- CXR and CT scan may reveal cavity formation.

Allergic Bronchopulmonary Aspergillosis
- Lab: peripheral eosinophilia, ↑ total serum IgE level, + Aspergillus serum precipitating Ab (70%-100%), + skin test w/Aspergillus antigenic extract (nonspecific), + sputum cultures for Aspergillus spp (nonspecific).
- CXR: variable from small patchy, fleeting infiltrates (commonly in upper lobes) to lobar consolidation or cavitation. Most pts eventually develop central bronchiectasis.

Aspergillomas
- Lab: sputum culture, serum precipitating Ab
- CXR or CT scan: intracavity mass partially surrounded by a crescent of air

Etiology
- Infection w/the Aspergillus species. Aspergillus fumigatus is the usual cause, A. flavus is the second most important species, particularly in invasive disease of immunosuppressed pts and in lesions beginning in the nose and paranasal sinuses.

Treatment
- Invasive aspergillosis:
  - Voriconazole 6 mg/kg IV q12h for 2 doses, then 4 mg/kg q12h PO Rx for adults is 200 mg bid or 4 mg/kg bid.
  - Caspofungin in pts who fail to respond to or are unable to tolerate other antifungal drugs. The recommended dosage is 70 mg on the first day and 50 mg qd thereafter given as a single dose IV over 1 hr.
- Allergic bronchopulmonary aspergillosis: prednisone (0.5-1 mg/kg PO) until the CXR has cleared, followed by alternate-day Rx at 0.5 mg/kg PO for 3-6 mo, then gradually tapered.
- Aspergillomas: surgical resection/arterial embolization for those pts w/severe hemoptysis or life-threatening hemorrhage. For those pts at risk for marked hemoptysis w/inadequate pulmonary reserve, consider itraconazole 200-400 mg/day PO.

59 ASTHMA

Definition
The National Asthma Education and Prevention Program (NAEPP) guidelines define asthma as “a chronic inflammatory disease of the airways in which many cells and cellular elements play a role: in particular mast cells, neutrophils, eosinophils, T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. The episodes are usually associated w/widespread but variable airflow obstruction that is reversible either spontaneously or as a result of treatment.”

Status asthmaticus can be defined as a severe continuous bronchospasm.

Diagnosis

H&P
- Evaluate for environmental causes (e.g., house dust mites, indoor pets) and exposure to other allergens such as tobacco smoke. For symptomatic adults and children aged >5 yr who can perform spirometry, asthma can be dx after an H&P documenting an episodic pattern of respiratory sx and from spirometry that indicates partially reversible airflow obstruction (>12% ↑ and 200 mL in 1 FEV1 after inhaling a short bronchodilator or receiving a short [2-3 wk] course of oral corticosteroids). For children aged <5 yr, spirometry is generally not feasible. Young children w/asthma sx
Chapter 3 Diseases and Disorders

Diseases

■ Should be treated as having suspected asthma once alternative diagnoses are ruled out.
■ The degree of reversibility measured by spirometry correlates w/airway obstruction, and pts w/a high degree of reversibility have a greater risk of irreversible airflow obstruction in subsequent years.
■ Following dx, classify severity of asthma before initiating Rx. The following questions from Asthma Control Test (ACT) and endorsed by the American Lung Association are important in assessing pts w/asthma:
  • Has your asthma prevented nl activities at home or work?
  • Have you had SOB in the past 4 wk?
  • Has your asthma kept you awake at night?
  • How often have you used your asthma inhaler in the last 4 wk?
  • Overall, how have you made your asthma control in the last 4 wk?
■ Once Rx is initiated, the emphasis for clinical management is changed to the assessment of asthma control. The level of asthma control should be used to guide decisions either to maintain or to adjust Rx.
■ PE: varies w/the stage and severity of asthma and may reveal only ↑ inspiratory and expiratory phases of respiration. PE during status asthmaticus may reveal:
  • Tachycardia and tachypnea
  • Use of accessory respiratory muscles
  • Pulsus paradoxus (inspiratory decline in systolic BP >10 mm Hg)
■ Wheezing: absence of wheezing (silent chest) or ↓ wheezing can indicate worsening obstruction.
■ ΔMS: generally secondary to hypoxia and hypercapnia and constitutes an indication for urgent intubation.
■ Paradoxical abd and diaphragmatic movement on inspiration (detected by palpation over the upper part of the abd in a semirecumbent position): important sign of impending respiratory crisis, indicates diaphragmatic fatigue.
■ The following abnormalities in VS are indicative of severe asthma:
  • Pulsus paradoxus >18 mm Hg
  • RR >30 breaths/min
  • Tachycardia w/HR >120 bpm

Labs
■ Usually not necessary and can be nl if obtained during a stable period
■ ABGs can be used in staging the severity of an asthmatic attack:
  • Mild: ↓ PaO₂ and PaCO₂, ↑ pH
  • Moderate: ↓ PaO₂, nl PaCO₂, nl pH
  • Severe: marked ↓ PaO₂, ↑ PaCO₂, and ↓ pH
■ CBC, leukocytosis w/“left shift” may indicate the existence of bacterial infection

PFTs and Spirometry
■ Spirometry is recommended at the initial assessment and at least every 1-2 yr after Rx is initiated and when the sx and peak expiratory flow have stabilized. Spirometry as a monitoring measure may be performed more frequently, if indicated, on the basis of severity of sx and the disease’s lack of response to Rx.
■ PFTs: during acute severe bronchospasm, FEV₁ is <1 L and peak expiratory flow rate (PEFR) <80 L/min.

Imaging
■ CXR: usually nl, may show evidence of thoracic hyperinflation (e.g., flattening of the diaphragm, ↑ volume over the retrosternal air space).
■ ECG: tachycardia, nonspecific ST-T wave changes are common during an asthmatic attack; may also show cor pulmonale, RBBB, RAD, counterclockwise rotation.

Etiology
■ Sx are more commonly due to specific (aeroallergens) or nonspecific (e.g., dust, cigarette smoke, fumes, cold air, exercise) exposures.
■ Traditionally, intrinsic asthma was described as occurring in pts who have no h/o allergies possibly triggered by URIs or psychological stress; and extrinsic asthma (allergic asthma), brought on by exposure to allergens (e.g., dust mites, cat allergen, industrial chemicals).
Exercise-induced asthma: seen most frequently in adolescents; manifested w/bronchospasm after initiation of exercise and improves w/discontinuation of exercise.

Drug-induced asthma: often associated w/use of NSAIDs, β-blockers, sulfites, certain foods and beverages.

There is a strong association of the ADAM33 gene w/asthma and bronchial hyperresponsiveness.

**Treatment**

The 2007 NAEPP guidelines are described in Table 3-5.

**Clinical Pearls**

- The differentiation of asthma from COPD can be challenging. A hx atopy and intermittent, reactive sx points toward a dx of asthma, whereas smoking and advanced age are more indicative of COPD. Spirometry is useful to distinguish asthma from COPD.

- In all asthma pts, it is important to treat or to prevent comorbid conditions (e.g., rhinosinusitis, vocal cord dysfunction, GERD).

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### 60 ASTROCYTOMA

**Definition**

Neuroepithelial tumor that arises from glial precursor cells (i.e., astrocytes, oligodendrocytes, ependymal cells, choroid plexus, and others). Astrocytoma arises from astrocytes within the CNS. They are commonly graded by the WHO or the St. Anne–Mayo grading system. The WHO grades astrocytomas as follows:

- **Grade I:** juvenile pilocytic astrocytoma, subependymal giant cell astrocytoma, and pleomorphic xanthoastrocytoma
- **Grade II:** low-grade astrocytoma (LGA), fibrillary infiltrating astrocytoma
- **Grade III:** anaplastic astrocytoma
- **Grade IV:** glioblastoma multiforme (GBM)

- Grades III and IV are considered high-grade (HGA) or malignant

  The Kernohan system grades astrocytomas based on histologic features: cellularity, mitoses, pleomorphism, vascularity, and necrosis.

- Grade I increased cellularity.
- Grade II > cellularity than Grade I + pleomorphism.
- Grade III > cellularity and pleomorphism than Grade II + vascular proliferation.
- Grade IV all of the above + necrosis and pseudopalisading.

**Diagnosis**

**H&P**

The presenting sx of astrocytoma depend, in part, on the location of the lesion and its rate of growth. Astrocytomas classically present w/one or more of the following features:

- Headache (less frequent)
- New-onset partial or generalized seizures (>50%)
- N/V
- Focal neurologic deficit (cranial nerve palsy, hemiplegia, ataxia)
- ΔMS
- Papilledema (rare)

**Labs**

- Blood tests are not very specific.

**Imaging**

- MRI and MRA are used to locate the margins of the tumor, to distinguish vascular masses from tumors, to detect low-grade astrocytomas not seen by CT scan, and to provide clear views of the posterior fossa.
- PET scanning and MR spectroscopy are newer imaging modalities that may be indicated in some pts to assess metabolic and vascular features of a tumor.

**Etiology**

- The specific etiology of astrocytoma is unknown.
- The only proven risk factor for development of astrocytoma has been significant exposure to ionizing radiation.
**TABLE 3-5  Stepwise Approach for Managing Asthma in Youths ≥12 yr and Adults**

<table>
<thead>
<tr>
<th>Intermittent Asthma</th>
<th>Persistent Asthma: Daily Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consult with asthma specialist if step 4 core or higher is required. Consider consultation at step 3.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
<th>Step 5</th>
<th>Step 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred: SABA PRN</td>
<td>Preferred: Low-dose ICS + LABA Alternative: Cromolyn, LTRA, nedocromil, or theophylline</td>
<td>Preferred: Low-dose ICS + LABA Alternative: Medium-dose ICS + either LTRA, theophylline, or zileuton</td>
<td>Preferred: Medium-dose ICS + LABA Alternative: Medium-dose ICS + either LTRA, theophylline, or zileuton</td>
<td>Preferred: High-dose ICS + LABA and Consider omalizumab for patients who have allergies</td>
<td>Step up if needed (first, check adherence, environmental control, and comorbid conditions) Assess control Step down if possible (and asthma is well controlled at least 3 months)</td>
</tr>
</tbody>
</table>

Each step: Patient education, environmental control, and management of comorbidities

Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma

Quick-Relief Medication for All Patients:
- SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.
- Use of SABA ≥2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.

The stepwise approach is meant to assist, not to replace, the clinical decision-making required to meet individual patient needs.

If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.

Zileuton is a less desirable alternative because of limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.

In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.

Steps 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR-2 1997) and Evidence B for omalizumab.

Immunotherapy for steps 2-4 is based on Evidence B for house dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.

Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and to treat anaphylaxis that may occur.

This information is directly abstracted from the 2007 NAEPP Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma and is not intended to promote or to endorse any of the listed products.

To access the complete Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, go to www.nhlbi.nih.gov/guidelines/asthma/asthgdin.pdf.

EIB, exercise-induced bronchospasm; ICS, inhaled corticosteroid; LABA, inhaled long-acting β₂-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting β₂-agonist.
Other risk factors, such as ↑ exposure to certain chemicals (petroleum, solvents, lead, pesticides and herbicides), have been proposed but not proved.

**Treatment**
- When there is evidence of ↑ ICP, initiation of IV mannitol followed by IV dexamethasone is indicated while waiting for surgical intervention.
- Mechanical ventilation w/hyperventilation may be considered if there is depressed consciousness.
- Surgery remains the initial treatment of almost all astrocytomas, particularly if the tumor is in an anatomically accessible location.
- Before surgery, dexamethasone 10 mg IV is given, followed by 4-6 mg IV q6h.
- Surgical morbidity and mortality are related to tumor location. Pts w/deep tumors or tumors in eloquent cortex are at high risk for neurologic deterioration from surgical resection or bx.
- Stereotactic radiosurgery: reserved for nonresectable lesions.
- Observation: may be justified if risks of surgical or radiation Rx are > risks of medical Rx of presenting sx.
- Single or recurrent seizures should be treated w/anticonvulsants. Common choices are phenytoin, valproate, carbamazepine, and levetiracetam. The last has no drug interactions compared w/the older antiepileptic medications.
- Chemotherapeutic drugs have been used w/some effect in pts w/high-grade astrocytoma. The addition of adjuvant chemotherapy in these pts has been shown to ↑ the proportion of long-term survivors from <5% to approximately 15%-20%.
- Current options for adjuvant chemotherapy include single-agent carmustine or temozolomide, the PCV regimen (procarbazine/lomustine/vincristine), and placement of Gliadel wafers into the resection cavity at the time of surgery.
- High-dose chemotherapy followed by autologous bone marrow transplantation is a consideration.

**Clinical Pearl**
- Postoperative radiation Rx is controversial in pts w/LGA but standard in high-grade astrocytoma. Some authorities recommend waiting for sx to occur after surgery in pts w/LGA before using radiation Rx.

### ATELECTASIS

**Definition**
Collaps of lung volume.

**Diagnosis**

**H&P**
- ↓ or absent breath sounds, abnl chest percussion, diminished chest expansion, tachypnea, tachycardia
- Cough, dyspnea, ↓ vocal fremitus and vocal resonance

**Imaging**
- CXR
- CT in pts w/suspected endobronchial neoplasm or extrinsic bronchial compression

**Etiology**
- Mechanical ventilation w/higher FiO₂
- Chronic bronchitis
- Cystic fibrosis
- Endobronchial neoplasms
- Foreign bodies
- Infections (e.g., TB, histoplasmosis)
- Extrinsic bronchial compression from neoplasms, aneurysms of ascending aorta, enlarged left atrium
- Sarcoïdosis
- Silicosis
- Anterior chest wall injury, pneumothorax, rib fix
Alveolar injury (e.g., toxic fumes, aspiration of gastric contents)
- Pleural effusion, expanding bullae
- Chest wall deformity (e.g., scoliosis)
- Muscle weaknesses or abnormalities (e.g., neuromuscular disease)
- Mucous plugs from asthma, allergic bronchopulmonary aspergillosis

**Treatment**
- Incentive spirometry, chest physiotherapy, humidification of inspired air, frequent nasotracheal suctioning
- Positive-pressure breathing (CPAP by face mask, PEEP for pts on mechanical ventilation)
- Use of mucolytic agents (e.g., acetylcysteine)
- Recombinant human DNase (dornase alfa) in pts w/cystic fibrosis
- Bronchodilator Rx in selected pts

**Clinical Pearls**
- Pts should be educated that frequent changes of position are helpful in clearing secretions. Sitting the pts upright in a chair is recommended to ↑ both volume and VC relative to the supine position.
- #1 cause of fever on postoperative day 1-2

## ATRIAL FIBRILLATION (AF)

### Definition
Totally chaotic atrial activity caused by simultaneous d/c of multiple atrial foci.

### Diagnosis

#### H&P
Clinical presentation is variable:
- Most common complaint: palpitations
- Fatigue, dizziness, lightheadedness in some pts
- A few completely asymptomatic pts
- Cardiac auscultation revealing irregularly irregular rhythm

#### Labs
- TSH, free T₄
- Serum electrolytes

#### Imaging
- ECG (Fig. 3-14)
  - Irregular, nonperiodic waveforms (best seen in V₁) reflecting continuous atrial reentry
  - Absence of P waves
  - Conducted QRS complexes showing no periodicity
- Echo: evaluate left atrial size and detect valvular disorders
- Holter monitor: useful only in selected pts to evaluate paroxysmal AF

![Atrial fibrillation](image)

**FIGURE 3-14.** Atrial fibrillation with slow ventricular response.

### Etiology
- CAD
- MS, MR, AS, AR
- Thyrotoxicosis
- PE, COPD
- Pericarditis
- Myocarditis, cardiomyopathy
- Tachy-brady syndrome
- Alcohol abuse
- MI
- WPW syndrome
- Obesity (the excess risk of AF associated w/obesity appears to be mediated by left atrial dilation)
ATRIAL FIBRILLATION (AF)

Treatment

New-onset AF

- Pt hemodynamically unstable: cardioversion after immediate conscious sedation w/a rapid short-acting sedative (e.g., midazolam)
- Pt hemodynamically stable, treatment options include the following:
  - Diltiazem 0.25 mg/kg given over 2 min followed by a second dose of 0.35 mg/kg 15 min later if the rate is not slowed. May then follow w/IV infusion 10 mg/hr (range, 5 to 15 mg/hr). Onset of action after IV administration is usually within 3 min, w/peak effect most often occurring within 10 min. After the ventricular rate is slowed, the pt can be changed to oral diltiazem 60-90 mg q6h.
  - Verapamil 2.5-5 mg IV initially, then 5-10 mg IV 10 min later if the rate is still not slowed. After the ventricular rate is slowed, the pt can be changed to PO verapamil 80-120 mg q6-8h.
  - Esmolol, metoprolol, and atenolol are β-blockers available in IV preparations that can be used in AF for rate control.
  - Other medications useful for converting AF to sinus rhythm are ibutilide, flecainide, propafenone, disopyramide, amiodarone, and quinidine.
- Digoxin is not a very potent AV nodal blocking agent and cannot be relied on for acute control of the ventricular response. When used, give 0.5 mg IV loading dose (slow), then 0.25 mg IV 6 hr later. A third dose may be needed after 6-8 hr; qd dose varies from 0.125-0.25 mg (↓ dose in pts w/renal insufficiency and elderly pts). Digoxin should be avoided in WPW pts w/AF. Procainamide is the preferred pharmacologic agent in these pts.
- IV heparin or SC LMWH
- Cardioversion is indicated if the ventricular rate is >140 bpm and the pt is symptomatic (particularly in acute MI, chest pain, dyspnea, CHF) or when there is no conversion to NSR after 3 days of pharmacologic Rx. The likelihood of cardioversion-related clinical thromboembolism is low in pts w/AF lasting <48 hr. Pts w/AF lasting >2 days have a 5%-7% risk of clinical thromboembolism if cardioversion is not preceded by several weeks of warfarin Rx. However, if TEE reveals no atrial thrombus, cardioversion may be performed safely after only a short period of anticoagulant Rx. Anticoagulant Rx should be continued for at least 1 mo after cardioversion to ↓ the incidence of adverse thromboembolic events after conversion from AF to sinus rhythm.

Anticoagulate w/warfarin (unless pt has specific contraindications).
- Long-term anticoagulation w/warfarin (adjusted to maintain an INR of 2-3) is indicated in all pts w/AF and associated CVD, including the following:
  - Rheumatic valvular disease (MS, MR, AI)
  - AS
  - Prosthetic heart valves
  - H/o previous embolism
  - Persistent atrial thrombus on TEE
  - CHF
  - Cardiomyopathy w/poor left ventricular function
  - Nonrheumatic heart disease (e.g., hypertensive CVD, CAD, ASD)
- Anticoagulation w/warfarin is generally not recommended in pts <60 yr w/lone AF (no associated CVD or diabetes). ASA at a dose of 325 mg/day is appropriate Rx in these pts.
- Clopidogrel + ASA may also be a suitable alternative to warfarin in pts who refuse warfarin or have contraindications to its use.

Medical Cardioversion

- Attempts at medical (pharmacologic) intervention should be considered only after proper anticoagulation because cardioversion can lead to
systemic emboli. After successful cardioversion, anticoagulation w/warfarin should be continued for 4 wk.

- Useful agents for medical cardioversion are procainamide, amiodarone, quinidine, flecainide, propafenone, ibutilide, sotalol, and dofetilide. Procainamide (total dose of 15 mg/kg given IV at 15-20 mg/kg) will restore sinus rhythm in 60% of pts w/AF of <1 wk duration. AV nodal blocking agents should be administered before using procainamide or any other primary antiarrhythmic agent to prevent conversion of AF into atrial flutter.

- Amiodarone appears to be the most effective agent for converting to sinus rhythm in pts who do not respond to other agents. Amiodarone Rx should be considered for pts w/recent AF and structural heart disease, particularly those w/left ventricular dysfunction. Amiodarone should also be considered for pts w/refractory conditions who do not have heart disease before Rx w/irreversible effects such as AV nodal ablation are attempted. Amiodarone is also effective in maintaining sinus rhythm in AF but is associated w/potentially serious toxic effects. Dronedarone is a new antiarrhythmic agent, pharmacologically related to amiodarone, that appears to be effective w/fewer side effects.

- Anticoagulant Rx should be continued for at least 1 mo after cardioversion w/antiarrhythmic drugs because pts may remain at risk, in the short term, for atrial clot formation even after restoration of sinus rhythm.

- Factors associated w/maintenance of sinus rhythm after cardioversion:
  - Left atrium diameter <60 mm
  - Absence of mitral valve disease
  - Short duration of AF

**Surgical Treatment of AF**

- The procedure w/recent modifications creating electrical barriers to the macroentrant circuits that are thought to underlie AF is being performed w/good results in several medical centers (preservation of sinus rhythm in >95% of pts w/o the use of long-term antiarrhythmic medication). Clear indications for its use remain undefined. In general, surgery is reserved for pts w/rapid HR refractory to pharmacologic Rx or who cannot tolerate pharmacologic Rx.

- Catheter-based radiofrequency ablation procedures designed to eliminate AF represent newer approaches to AF. Restoration and maintenance of sinus rhythm by catheter ablation w/o the use of drugs in pts w/CHF and AF significantly improve cardiac function, sx, exercise capacity, and quality of life.

- Pulmonary vein ablation for chronic AF: sinus rhythm can also be maintained long term in the majority of pts w/chronic AF by means of circumferential pulmonary vein ablation, independently of the effects of antiarrhythmic drug Rx, cardioversion, or both.

- Implantable pacemakers and defibrillators that combine pacing and cardioversion Rx are likely to have an ↑ role in the future management of AF.

**Clinical Pearls**

The American Academy of Family Physicians and the American College of Physicians provide the following recommendations for the management of newly detected AF:

- Rate control w/chronic anticoagulation is the recommended strategy for the majority of pts w/AF. Rhythm control has not been shown to be superior to rate control (w/chronic anticoagulation) in reducing morbidity and mortality and may be inferior to rate control in some pt subgroups. Rhythm control is appropriate when based on other special considerations, such as pt sx, exercise tolerance, and pt preference.

- Pts w/AF should receive chronic anticoagulation w/adjusted-dose warfarin, unless they are at low risk of stroke or have a specific contraindication to the use of warfarin (allergy to medication, thrombocytopenia, recent trauma or surgery, alcoholism).

- For pts w/AF, the following drugs are recommended for their demonstrated efficacy in rate control during exercise and while at rest: atenolol, metoprolol, diltiazem, and verapamil (drugs listed alphabetically by class). Digoxin is effective for rate control only at rest and therefore should be used only as a second-line agent for rate control in AF.
For those pts who elect to undergo acute cardioversion to achieve sinus rhythm in AF, both direct-current cardioversion and pharmacologic conversion are appropriate options.

Both TEE w/short-term prior anticoagulation followed by early acute cardioversion (in absence of intracardiac thrombus) w/post-cardioversion anticoagulation and delayed cardioversion w/pre- and post-anticoagulation are appropriate management strategies for those pts who elect to undergo cardioversion.

Most pts converted to sinus rhythm from AF should not be prescribed rhythm maintenance Rx because the risks outweigh the benefits. In a selected group of pts whose quality of life is compromised by AF, the recommended pharmacologic agents for rhythm maintenance are amiodarone, disopyramide, propafenone, and sotalol (drugs listed in alphabetical order). The choice of agent depends on specific risk of side effects based on pt characteristics.

In pts w/AF and CHF, a routine strategy of rhythm control does not reduce the rate of death from CV causes compared w/a rate-control strategy.

### ATRIAL FLUTTER

**Definition**

Rapid atrial rate of 250-300 bpm w/various degrees of intraventricular block.

**Diagnosis**

**H&P**

- Fast pulse rate (approximately 150 bpm)
- Dyspnea, lightheadedness, chest pain

**Labs**

- TSH, free T4, serum electrolytes

**ECG (Fig. 3-15)**

- Regular, sawtooth, or F wave pattern, best seen in II, III, and aVF and secondary to atrial depolarization; AV conduction block (2:1, 3:1, or varying)

**Figure 3-15.** Atrial flutter waves (F). A, The flutter waves are not apparent in lead I but are obvious in leads II and III. B, Carotid sinus pressure slowed the ventricular rate but did not change the atrial flutter rate.
Etiology
- CAD
- MI
- Thyrotoxicosis
- PE
- Mitral valve disease
- Cardiac surgery
- COPD

Treatment
- Valsalva maneuver or carotid sinus massage usually slows the ventricular rate (↑ grade of AV block) and may make flutter waves more evident.
- DC cardioversion: Rx of choice for acute management of atrial flutter. Electrical cardioversion is given at low energy levels (20-25 J). Sedation of a conscious pt is highly recommended before cardioversion is performed.
- Overdrive pacing in the atrium may also terminate atrial flutter. This method is especially useful in pts who have recently undergone cardiac surgery and still have temporary atrial pacing wires.
- In absence of cardioversion, IV diltiazem or digitalization may be tried to slow the ventricular rate and to convert flutter to fibrillation. Esmolol, verapamil, and adenosine may also be effective. In pts w/atrial flutter, it is essential to preadminister AV nodal blocking agents before using procainamide or ibutilide.
- Atrial flutter is frequently associated w/intermittent AF. It may be prudent to anticoagulate pts w/atrial flutter and coexisting medical disorders (e.g., DM, HTN, cardiac disease) before cardioversion. Anticoagulation should also be considered for all pts w/atrial flutter who are older than 65 yr.
- Chronic atrial flutter may respond to amiodarone.
- Radiofrequency ablation to interrupt the atrial flutter is effective for pts w/chronic or recurring atrial flutter and is generally considered first-line Rx in those w/recurrent episodes of atrial flutter.

Clinical Pearls
- Atrial flutter is common during the first week after open heart surgery.
- Lone atrial flutter has a stroke risk at least as high as lone AF and carries an ↑ risk for subsequent development of AF than in the general population.
- Anticoagulation should be considered for all pts w/atrial flutter who are older than 65 yr.

Atrial Myxoma

Definition
Benign neoplasm of mesenchymal origin. It is the most common primary tumor of the heart.

Diagnosis
H&P
Pts w/atrial myxomas characteristically present in one of three ways:
- AV valve obstruction [e.g., mitral or tricuspid valve]: dyspnea, orthopnea, PND, edema, dizziness, syncope, ↑ JVP, loud S1, secondary pulmonary HTN, murmurs of regurgitation (holosystolic) or stenosis (rumbles), third heart sound “tumor plop,” AF
- Systemic embolization: leading to CVAs, PE, paradoxical embolism
- Constitutional sx: fever, weight loss, arthralgias, RP

Labs
- CBC: anemia, polycythemia, thrombocytopenia
- ↑ ESR, C-reactive protein, and serum immunoglobulins

Imaging
- ECG: left or right atrial enlargement, AF, PVCs, VT
- Echo: initial test of choice; TEE may better define cardiac masses not clearly visualized by TTE
- CXR: altered cardiac contour and chamber enlargement
- MRI: delineates size, shape, and tumor characterizations
- Cardiac cath: may be required to r/o concomitant CAD in anticipation to surgical excision of the tumor
Etiology
- Most cases (90%) of atrial myxomas are sporadic w/o known cause.
- In the remaining 10% of cases, a familial pattern occurs, having an autosomal dominant transmission known as the Carney complex (myxomas of the heart, skin, and breast; skin pigmentation; endocrine tumors; and schwannomas).

Treatment
- Surgical excision
- Surgery should be done promptly because systemic embolization or sudden death can occur.
- Treatment of constitutional and cardiac sx: diuresis, HR and BP control, and fever control

Clinical Pearls
- Approximately 75% of myxomas arise from the left atrium close to the fossa ovalis.
- Approximately 3/4 of pts present w/CV sx, specifically dyspnea, often suggestive of valvular obstruction.
- Nearly 1/3 of pts have evidence of systemic embolization.

ATRIAL SEPTAL DEFECT (ASD)

Definition
Abnl opening in the atrial septum that allows blood flow between the atria. There are several forms:
- Ostium primum: defect low in the septum
- Ostium secundum: occurs mainly in the region of the fossa ovalis
- Sinus venosus defect: less common form, involves the upper part of the septum

Diagnosis
H&P
- Exertional dyspnea may be present; however, pts w/small defects are generally asymptomatic.
- Pansystolic murmur best heard at apex secondary to MR (ostium primum defect), widely split S₂, visible and palpable pulmonary artery pulsations, ejection systolic flow murmur, prominent right ventricular impulse, cyanosis, and clubbing (severe cases)

Imaging
- Echo w/saline bubble contrast and Doppler flow studies: may demonstrate the defect and the presence of shunting. TEE is much more sensitive than TTE in identifying sinus venosus defects and is preferred by some for the initial diagnostic evaluation.
- Cardiac cath: confirms the dx in pts who are candidates for surgery. It is useful if the pt has some anatomic finding on echo that is not completely clear or has significant elevation of PAPs.

ECG
- Ostium primum defect: LAD, RBBB, prolongation of PR interval
- Sinus venosus defect: leftward deviation of P axis
- Ostium secundum defect: RAD, RBBB

Etiology
- Unknown

Treatment
- Children and infants: closure of ASD before age 10 yr is indicated if pulmonary-systemic flow ratio is >1.5:1.
- Adults: closure is indicated in symptomatic pts w/shunts >2:1.
- Surgery should be avoided in pts w/pulmonary HTN w/reversed shunting (Eisenmenger’s syndrome) because of ↑ risk of right-sided heart failure.
- Transcatheter closure in children when feasible
- Prophylactic β-blocker Rx to prevent atrial arrhythmias in adults w/ASD
- Surgical closure is indicated in all pts w/ostium primum defect and significant shunting unless pt has significant pulmonary vascular disease.
Clinical Pearls

- Surgical mortality varies w/ the age of the pt and the presence of cardiac failure and systolic pulmonary artery HTN; mortality ranges from <1% in young pts (<45 yr) to >10% in elderly pts w/ presence of heart failure and systolic pulmonary HTN.
- Preoperative AF is a risk factor for immediate postoperative and long-term AF.

66 BABESIOSIS

Definition

A tick-transmitted protozoan disease of animals, caused by intraerythrocytic parasites of the genus Babesia. Humans are incidentally infected, resulting in a nonspecific febrile illness.

Diagnosis

H&P

- Clinical presentation: incubation period 1-4 wk, or 6-9 wk in transfusion-associated disease. Gradual onset of irregular fever, chills, diaphoresis, headache, myalgia, arthralgia, fatigue, and dark urine.
- PE: petechiae, frank or mild hepatosplenomegaly, and jaundice. Infection w/ B. divergens produces a more severe illness w/ a rapid onset of sx and ↑ parasitemia progressing to massive intravascular hemolysis and renal failure.

Labs

- Dx achieved serologically by indirect IFA is specific for B. microti.
- Titer of ≥1:64 is indicative of seropositivity, whereas one ≥1:256 is considered diagnostic of acute infection.
- Immunoglobulin M indirect immunofluorescent Ab test may be highly sensitive and specific for dx.
- Babesial DNA by PCR has sensitivity and specificity comparable to microscopic analysis of thin blood smears.
- Examination of Giemsa- or Wright-stained thick and thin blood films for intraerythrocytic parasites. In its classic although infrequently seen form, a tetrad or Maltese cross composed of four daughter cells attached by cytoplasmic strands is observed. More commonly, smaller forms composed of a single chromatin dot are eccentrically located within bluish cytoplasm.

Treatment

- Combination of atovaquone 750 mg q12h and azithromycin 500 mg on day 1 and 250 mg per day thereafter for 7 days is preferred Rx.
- Combination of quinine sulfate 650 mg PO tid plus clindamycin 600 mg PO tid (1.2 g parenterally bid) taken for 7-10 days
- Exchange transfusions in addition to antimicrobial Rx: successful treatment of severe infections in asplenic pts associated w/ high levels of B. microti or B. divergens parasitemia

67 BALANITIS

Definition

Inflammation of the superficial tissues of the penile head.

Diagnosis

H&P

- Itching and tenderness, pain, dysuria, and local edema. Rarely, ulceration and lymph node enlargement may be present. Severe ulcerations can lead to superimposed bacterial infections.

Etiology

- Poor hygiene causing erosion of tissue w/ erythema and promoting growth of Candida albicans
- Sexual contact, urinary catheters, and trauma
- Allergic reactions to condoms or medications

Treatment

- Fluconazole 150 mg PO × 1 or itraconazole 200 mg PO bid × 1 day
- Retraction and bathing of prepuce several times a day in uncircumcised males
Warm sitz baths to ease edema and erythema
Consideration of circumcision, especially when sx are severe or recurrent
Consider bx to r/o other dx such as premalignant or malignant lesions if lesions are not healing

68 BARBITURATE OVERDOSE

Diagnosis

H&P
- Lethargy, respiratory depression, coma
- ↓ DTRs, extensor plantar response

Labs
- BMP, LFTs, Ca, Mg, PO4
- Serum and urine toxicology screen; ethanol, ASA, and acetaminophen level

Imaging
- CXR, ECG

Treatment
- IV bolus NaHCO3, 2 mEq/kg IV push, then start maintenance infusion (132 mEq NaHCO3 in 1 L D5W at 250 mL/hr)
- Administration of activated charcoal (0.5-1 g/kg; max: up to 50 g PO) in water or sorbitol by NG tube
- Gastric lavage w/early presentation
- Hemoperfusion

Clinical Pearl
- Avoid inducing emesis.

69 BARRETT’S ESOPHAGUS

Definition
Columnar metaplasia of the lower esophagus due to chronic acid reflux associated w/↑ risk of esophageal adenocarcinoma.

Diagnosis

H&P
- Sx: heartburn, dysphagia for solid food, chest pain, hematemesis

EGD
- Endoscopy w/bx necessary for dx. Dx requires the presence of intestinal metaplasia in columnar epithelium displaced proximal to the gastrosophageal junction.

Etiology
- Metaplasia is thought to result from re-epithelialization of esophageal tissue injured secondary to chronic gastrosophageal reflux.

Treatment
- PPIs are most effective at relieving sx and healing mucosal injury.
- Nissen fundoplication may be considered for management of GERD and associated sequelae. Endoscopic eradication therapy or surgical esophagectomy is offered for multifocal high-grade dysplasia.

Clinical Pearls
- Only 4%-10% of pts w/reflux sx develop Barrett’s esophagus.
- Pts w/chronic GERD sx should be considered for a one-time endoscopy to exclude the presence of Barrett’s esophagus. Because many pts w/Barrett’s esophagus are asymptomatic, some will be missed; however, general population screening is not currently recommended.
- Intestinal metaplasia of the gastric cardia is not considered Barrett’s esophagus and does not appear to convey the same risk of malignant transformation.

70 BARTTER’S SYNDROME

Definition
Group of renal tubular disorders characterized by metabolic alkalosis, hypokalemia, hyperplasia of the juxtaglomerular apparatus, hyperreninemic hyperaldosteronism, and hypercalciiura.
**Diagnosis**

**H&P**
Classic Bartter’s syndrome may include a h/o maternal polyhydramnios and premature delivery. The following features are characteristic:
- Polyuria
- Polydipsia
- Hypokalemia
- Metabolic alkalosis
- Hypercalciuria
- Plasma Mg: nl/↓
- Pts are normotensive.
- Pts do not have edema.

**Labs**
- Serum sodium, potassium, chloride, bicarbonate, Ca, Mg, phosphorus
- Urine Ca, chloride, assay for diuretics
- Serum pH can be confirmed by performing ABG

**Imaging**
- Renal U/S may show nephrocalcinosis, hydronephrosis, and hydroureter in neonatal Bartter’s syndrome.

**Etiology**
- Disorder of chloride reabsorption in the thick ascending loop of Henle
- A couple of defects manifest the same phenotype.
- Tubular pathophysiology is identical to loop diuretic mechanism of action.

**Treatment**
- Usual treatment includes oral potassium and Mg supplementation, although achievement of nl serum potassium and Mg levels is often difficult.
- Potassium-sparing diuretics, such as spironolactone and amiloride, have also been used effectively in the treatment of Bartter’s syndrome.

**Clinical Pearls**
- Just as Bartter’s syndrome looks like loop diuretic use from the point of view of laboratory testing, Gitelman’s syndrome appears identical to thiazide use.
- ↑ Urine Ca is the best way to distinguish Bartter’s syndrome from Gitelman’s syndrome.

## BEHÇET’S SYNDROME

**Definition**
Chronic, relapsing, inflammatory disorder characterized by the presence of recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions.

**Diagnosis**
- Dx is clinical. Labs and imaging may be helpful in working up the complications of Behçet’s disease or excluding other diseases in the diff.
- According to the International Study Group for Behçet’s disease, the diagnosis of Behçet’s disease is established when recurrent oral ulceration is present along w/at least two of the following in the absence of other systemic diseases:
  - Recurrent genital ulceration
  - Eye lesions
  - Skin lesions
  - Positive pathergy test result

**Treatment**

**Oral and Genital Ulcers**
- Topical corticosteroids (e.g., triamcinolone acetonide ointment applied tid)
- Tetracycline tablets 250 mg dissolved in 5 mL water and applied to the ulcer for 2-3 min
- Colchicine 0.5-1.5 mg/day PO
- Thalidomide 100-300 mg PO qd
- Dapsone 100 mg PO qd
- Pentoxifylline 300 mg/day PO
Azathioprine 1-2.5 mg/kg/day PO
MTX 7.5-25 mg/wk PO or IV

Ocular Lesions
- Anterior uveitis: topical corticosteroids (e.g., betamethasone drops, 1-2 drops tid); topical injection w/dexamethasone 1-1.5 mg has also been tried
- Infliximab 5 mg/kg single dose
- CNS disease
  - Chlorambucil 0.1 mg/kg/day is used in the treatment of posterior uveitis, retinal vasculitis, or CNS disease.Pts not responding to chlorambucil can try cyclosporine 5-7 mg/kg/day.
  - CNS vasculitis: cyclophosphamide 2-3 mg/kg/day. Prednisone can be used as an alternative.

Arthritis
- NSAIDs (e.g., ibuprofen 400-800 mg tid PO or indomethacin 50-75 mg/day PO)
- Sulfasalazine 1-3 g/day PO is an alternative treatment.

GI Lesions
- Sulfasalazine 1-3 g/day PO
- Prednisone 40-60 mg/day PO

Vascular Lesions
- Prednisone 40-60 mg/day PO
- Cytotoxic agents as mentioned previously
- Heparin 5000-20,000 U/day followed by oral warfarin

BELL’S PALSY

Definition
Idiopathic, isolated, usually unilateral facial weakness in the distribution of the seventh cranial nerve (<1% of the facial palsies are bilateral).

Diagnosis
H&P
- Unilateral paralysis of the upper and lower facial muscles (asymmetric eye closure, brow, and smile); upward rolling of eye on attempted eye closure (Bell’s phenomenon)
- Ipsilateral loss of taste
- Ipsilateral ear pain, usually 2-3 days before presentation
- ↑ or ↓ unilateral eye tearing
- Hyperacusis
- Subjective (but not objective) ipsilateral facial numbness

Labs
- FBS to evaluate for diabetes. Lyme titer in endemic areas. Consider CBC, VDRL, ESR, in selected pts.

Imaging
- Contrast-enhanced MRI to exclude neoplasms is indicated only in pts w/atypical features or course.
- CXR may be useful to exclude sarcoidosis or to r/o TB in selected pts before treatment w/steroids.

Etiology
- Most cases are idiopathic.
- The cause is often viral (HSV).
- Herpes zoster can cause Bell’s palsy in association w/herpetic blisters affecting the outer ear canal or the area behind the ear (Ramsay-Hunt syndrome).
- Bell’s palsy can also be one of the manifestations of Lyme disease.

Treatment
- Although the benefits of corticosteroid Rx remain unproven, most practitioners use a brief course of prednisone Rx. Combination Rx w/acyclovir and prednisone is not more effective than prednisone alone in improving clinical recovery.
- If used, prednisone Rx should be started within 24-48 hr of sx onset.
Chapter 3  Diseases and Disorders

Avoid corneal drying by applying skin tape to the upper lid to keep the palpebral fissure narrowed. Lacri-Lube ophthalmic ointment at night and artificial tears during the day are also useful to prevent excessive drying.

Use dark glasses when going outside to minimize sun exposure.

Botulinum toxin may be helpful for treatment of synkinesis and hemifacial spasm, two late sequelae of Bell’s palsy.

Clinical Pearls

- Pts should be monitored for evidence of corneal abrasion and ulceration or hemifacial spasm. Physical Rx including moist heat and massage may be beneficial.
- 71% of pts should recover completely. Prognosis is improved for those w/clinical improvement within 3 wk and w/less severity of sx at onset.
- Ensure that both upper and lower aspects of the face are involved (as this suggests a peripheral lesion). Lower facial asymmetry alone is more likely central (e.g., stroke), and further w/u is necessary.

**73 BENZODIAZEPINE OVERDOSE**

**Diagnosis**

**H&P**

- Delirium, dizziness, lethargy, respiratory depression, psychomotor agitation, slurred speech, hypothermia, tachycardia, seizures

**Labs**

- BMP, LFTs, Ca, Mg, PO₄
- Serum and urine toxicology screen; ethanol, ASA, and acetaminophen level

**Imaging**

- CXR, ECG

**Treatment**

- Early presentation: activated charcoal (50 g in H₂O or sorbitol by NG tube)
- Flumazenil 0.2 mg IV over 30 sec, may repeat w/0.3 mg 1 min later and 0.5 mg 1 min later (max total dose is 5 mg)—use w/caution in chronic benzo users (may cause seizures)

**74 BITE WOUNDS**

**Definition**

A bite wound can be animal or human, accidental or intentional.

**Diagnosis**

**H&P**

- The appearance of the bite wound is variable (e.g., puncture wound, tear, avulsion).
- Cellulitis, lymphangitis, and focal adenopathy may be present in infected bite wounds.
- Pt may experience fever and chills.

**Labs**

- Generally not necessary. Wound cultures (aerobic and anaerobic) if there is evidence of sepsis or victim is immunocompromised pt; cultures should be obtained before irrigation of the wound but after superficial cleaning. Consider CBC if there has been significant blood loss.

**Imaging**

- X-rays are indicated when bone penetration is suspected or if there is suspicion of fx or significant trauma; x-rays are also useful for detecting presence of foreign bodies (when suspected).

**Etiology**

Most frequent infecting organisms:

- *Pasteurella* spp: responsible for majority of infections within 24 hr of dog (*P. canis*) and cat (*P. multocida, P. septica*) bites
- *Capnocytophaga canimorsus* (formerly DF-2 bacillus): a gram-negative organism responsible for late infection, usually after dog bites
- Gram-negative organisms (*Pseudomonas, Haemophilus*): often found in human bites
- *Streptococcus* spp, *Staphylococcus aureus*
- *Eikenella corrodens* in human bites
**Treatment**
- Local care w/debridement, vigorous cleansing, and saline irrigation of the wound; debridement of devitalized tissue. Operating room for washout of human bites w/tendon involvement.
- High-pressure irrigation to clean bite wound and to ensure removal of contaminants (e.g., use saline solution w/30- to 35-mL syringe equipped w/20-gauge needle or catheter w/tip of syringe placed 2-3 cm above the wound)
- Avoid blunt probing of wounds (↑ risk of infection).
- Avoid suturing of hand wounds and any wounds that appear infected.
- Puncture wounds should be left open.
- Give antirabies Rx and tetanus immune globulin (250-500 units IM in limb contralateral to toxoid) and toxoid (adult or child >5 yr, 0.5 mL DT given IM; child <5 yr, 0.5 mL DPT IM) PRN.
- Use empiric abx Rx in high-risk wounds (e.g., cat bite, hand bites, face bites, genital area bites, bites w/joint or bone penetration, human bites, immunocompromised host): amoxicillin-clavulanate 500-2000 mg bid for 7 days or cefuroxime 250-500 mg bid for 7 days.
- In hospitalized pts, IV abx of choice are cefoxitin 1-2 g q6h, ampicillin-sulbactam 1.5-3 g q6h, ticarcillin-clavulanate 3 g q6h, and ceftriaxone 1-2 g q24h.
- Prophylactic Rx for persons bitten by others w/HIV infection and hepatitis B.

**Clinical Pearl**
- Infection rates are highest for cat bites (30%-50%), followed by human bites (15%-30%) and dog bites (5%).

**75 BITES AND STINGS, ARACHNIDS**

**Definition**
There are two major classes of arthropods: insects and arachnids. This topic focuses on the class Arachnida. Arachnid bites consist of bites caused by:
- Spiders
- Scorpions
- Ticks

**Diagnosis**

**Spiders**
- Sydney funnel web—atrataxin toxin: piloerection, muscle spasms leading to tachycardia, HTN, ↑ ICP, coma
- Black widow—females toxic
  - Initial reaction: local swelling, redness (two fang marks) leading to local piloerection, edema, urticaria, diaphoresis, lymphangitis
  - Pain in limb leading to rest of body (chest pain, abd pain), compartment syndrome
- Brown recluse
  - Minor sting or burn
  - Wound may become pruritic and red w/blanched center w/vesicle; can necrose, especially in fatty areas; leaves eschar, which sloughs and leaves ulcer; can take months to heal
  - Systemic sx: headache, fever, chills, GI upset, hemolysis, renal tubular necrosis, DIC possible

**Scorpions**
- Sting leading to sympathetic and parasympathetic stimulation: HTN, bradycardia, vasoconstriction, pulmonary edema, reduced coronary blood flow, priapism, inhibition of insulin
- Also possible: tachycardia, arrhythmia, vasodilation, bronchial relaxation, excessive salivation, vomiting, sweating, bronchoconstriction, pancreatitis

**Ticks: U.S., Europe, Asia**
- Very small (<1 mm); usually must be attached >36 hr to transmit disease
- Lyme disease—most common
- Early: erythema migrans 60%-80% of cases
- 7-10 days: mild to moderate constitutional sx—disseminated; secondary skin lesions, fever, adenopathy, constitutional sx, facial palsy, peripheral
neuropathy, lymphocytic meningitis, meningoencephalitis, cardiac manifestations (heart block)
• Late: chronic arthritis, dermatitis, neuropathy, keratitis

Treatment

Spiders
• Sydney funnel web: pressure, immobilization immediately, supportive care, antivenin
• Black widow
  • Treatment is based on severity of sx. Bite is rarely fatal.
  • All should receive oxygen, IV, cardiac monitor, tetanus prophylaxis.
  • Symptomatic/supportive Rx
  • 10% Ca gluconate for muscle cramps (controversial)
  • Antivenin only for more severe reactions
    • Antivenin carries risk of anaphylaxis
      • Dose: one vial in 100 mL 0.9% saline during 20–30 min
      • Skin test before use
      • Give antihistamines w/use
• Brown recluse
  • Pain management, tetanus, supportive treatment
  • No consensus regarding best treatment; some evidence for hyperbaric oxygen

Scorpions
• Fluids, supportive care, species-specific antivenin (equine based, risk of serum sickness)—controversial

Ticks
• Prophylactic: tick >36 hr → single dose of doxycycline 200 mg
• Early localized disease
  • Treatment of choice in children: amoxicillin × 14 days
  • Doxycycline preferred in pts w/possible concurrent ehrlichiosis
• Early disseminated: treatment depends on manifestation
• Late disease: may require longer term/IV Rx; controversial for neurologic disease

Clinical Pearl
• Identification of spider should not be based on pt hx (many look-alikes); spider should be brought into medical facility to be identified.

76 BITES AND STINGS, INSECT

Definition
Most stinging insects belong to the Hymenoptera order and include yellow jackets (most common cause of reactions), hornets, bumble bees, sweat bees, wasps, harvester ants, fire ants, and the Africanized honey bee (killer bee). Brown recluse spiders, although they are not insects, are another common cause of bites (see Bites and Stings, Arachnids). The usual effect of a sting is intense local pain, some immediate erythema, and often a small area of edema by injecting venom. Allergic reactions can be either local or generalized, leading to anaphylactic shock. The majority of reactions occur within the first 6 hr after the sting or bite, but a delayed presentation may occur up to 24 hr.

Diagnosis

H&P
• Stings:
  • Cutaneous: the skin is the most common site of an allergic reaction. Manifestations include flushing, urticaria, pruritus, and angioedema.
  • Respiratory: hoarseness, difficulty speaking, choking; throat tightness or tingling may progress to stridor, laryngeal edema, laryngospasm, and bronchoconstriction. This is the leading cause of anaphylactic death.
  • CV: tachycardia, hypotension, arrhythmia; can progress to profound hypovolemic shock. MI is rare. Cardiac manifestations are the second leading cause of death from anaphylaxis.
  • Other sx: abd pain, N/V, and diarrhea
Fire ant bites:
- Initial wheal and flare response
- Subsequent development of circularly arrayed blisters within 24 hr
- Blisters may develop appearance of pustules, but they are not infected.

**Labs**
- Skin test: either skin prick test or intradermal method w/fire ant or hymenoptera venom
- Venom skin tests and occasionally radioallergosorbent tests (RAST) to provide additional information

**Etiology**

**Stings**
- Most systemic reactions to insect stings are classic IgE-mediated reactions.
- Reactions occur in previously sensitized pts who have produced high titers of IgE Ab to insect venom antigens.
- Sensitization to wasp venom requires only a few stings and can occur after a single sting.
- Sensitization to bee venom occurs mainly in people who have been stung frequently by bees.

**Bites**
- Fire ant venom contains proteins toxic to the skin.

**Treatment**

**Sting**
- Removal of the stinger is most readily performed w/flat tool like a credit card, cleansing, and application of ice.
- Rx w/PO antihistamines and NSAIDs for limited reactions; topical corticosteroids may provide some relief of inflammation.
- Pts w/previous reactions or multiple stings to the mouth or neck should be evaluated in an emergency department.
- Larger swellings may benefit from oral steroids.
- Generalized reactions should be treated w/epinephrine; antihistamines, oxygen, IV corticosteroids, β agonists, pressors, and IV fluids may also be beneficial for anaphylaxis.

**Bite**
- Supportive care
- Application of ice
- Surveillance for secondary infection

**Clinical Pearl**
- Hypersensitivity to stings is common. Reactions range from local nonallergic reaction to venom to life-threatening anaphylaxis. Venom-specific immunotherapy is highly effective in ↓ subsequent reactions.

**Bites, Snakes**

**Diagnosis**

In addition to local tissue injury, envenomation may affect the renal, neurologic, GI, vascular, and coagulation systems. Species-specific signs and sx include those listed in the following.

**Crotalidae (pit vipers)**
- Fang punctures
- Pain within 5 min
- Edema within 30 min
- Erythema of site and adjacent tissues/serous or hemorrhagic bullae, ecchymosis or lymphangitis during the ensuing hours
- If no edema or erythema is manifested within 8 hr after a confirmed crotalid snakebite, it is safe to assume envenomation did not occur (roughly 25% of cases do not involve envenomation).
- Systemic manifestations may include the following:
  - Mild to moderate manifestations: N/V, perioral paresthesias, metallic taste, tingling of fingers or toes (especially w/rattlesnake bites), fasciculations (local or generalized)
  - Severe manifestations: hypotension (due to ↑ vascular permeability), ΔMS, respiratory distress, tachycardia, ARF, rhabdo, intravascular hemolysis, DIC
**Elapidae (coral snakes)**

- Local sx are far less pronounced (little or no pain/swelling immediately after the bite).
- Systemic sx predominate, but onset may be delayed for up to 12 hr; examples include
  - Cranial nerve palsies featuring ptosis, dysphagia, or dysarthria
  - Tremors
  - Intense salivation

**Treatment**

- Establish IV access.
- Initiate reconstitution of appropriate antivenom. (Antivenoms are typically supplied in powder form and must be reconstituted before administration. The process can take up to 1 hr, so it is recommended that it be initiated as soon as the pt arrives in the emergency department). While this is being done:
  - Obtain time of bite and description of snake if possible.
  - Obtain PMHx; ask about allergies to horse serum in those previously treated for snakebite.
  - Record VS: BP, HR, T, RR.
  - Inspect site of bite for fang marks, local sx.
  - Delineate margins of erythema/edema w/a marker.
  - Measure circumferrence of bitten part at two or more proximal sites and compare w/unaffected limb; repeat every 15-20 min; assess for extension of erythema/edema.
  - Neurologic examination
  - Gauge the severity of the bite and decide whether administration of antivenom is necessary.
- For min. envenomation w/o progressive manifestations:
  - Clean and immobilize affected part.
  - Immunize against tetanus.
  - Observe pt for at least 8 hr. If, at the end of this interval, local and systemic sequelae are absent and lab values remain nl, the likelihood of significant envenomation is low, and the pt can be discharged from the acute setting.
- Pts who have progressive sx (local or systemic) or moderate to severe envenomation should be considered for antivenom. The high incidence of allergic reactions argues against its use in less severe cases.
- Antivenom is most effective when given within 4 hr of the bite and least effective if delayed beyond 12 hr. Systemic sx (coagulopathy, CNS effects) respond better to treatment than local sx (erythema/edema, bullae).
- It is recommended that pts be monitored in an ICU setting during administration of antivenom.
- Once the decision is made to use antivenom, prepare epinephrine 0.5-1.0 mL of a 0.1% solution to be administered in case of a hypersensitivity reaction to the antivenom. (Prophylactic antihistamines are not efficacious.)

**Treatment of crotalid (pit viper) bites w/sheep immunoglobulin–based antivenom:**

- Most centers now have sheep immunoglobulin–based antivenom (Crofab) for crotalid bites. (A potent, safe, sheep-based antivenom for elapid bites exists but is not yet approved in the U.S.) Sheep-based antivenoms are safe, but repeated administration may be necessary because of a short half-life. An initial IV loading dose of 4-6 vials (depending on the size and age of the pt and the severity of the bite) is infused during 60 min. If the pt has not responded after 1 hr, a repeated dose of 4-6 vials is indicated.
- Because of the short half-life of sheep-based antivenom, relapse may occur in up to two thirds of pts after an initial response. Consequently, it is recommended that three maintenance doses—each consisting of 2 vials—be given at 6, 12, and 18 hr after the pt’s initial response to the loading dose.
- Help in using the antivenom is available 24/7 by calling 877-377-3784.
Treatment of crotalid (pit viper) or elapid (coral snake) bites w/horse serum–based antivenom:
- Horse serum–based antivenoms are available for both crotalid and elapid (coral snake) bites, but it runs a much higher risk of hypersensitivity reactions, such as anaphylaxis and serum sickness. (Skin testing is available, but it is not recommended because it is not completely reliable and may delay time to administration beyond the most effective period.)
- For pit viper bites
  - Mild: 5 vials
  - Moderate: 10 vials
  - Severe: 15 vials
  - Shock: 20 vials
- For confirmed coral snake bites, antivenom (different formulation) should be administered immediately. If coral snake bite is only suspected, the pt should be monitored for 12 hr for evidence of envenomation and treated if it occurs.
- If there are no systemic sx at the time of administration, start w/3 vials. If sx evolve, repeat w/5 vials.
- If systemic sx are already present, an initial dose of 6-10 vials is recommended.

Treatment of non-native (exotic) snake bites:
- For bites by exotic or non-native snakes, contact a poison control center or your local zoo. (Zoos w/exotic snakes are required to maintain a supply of snake-specific antivenom on their premises.)
- Other considerations:
  - Initial dose of antivenom should be repeated until progression of sx has abated, but observation of bitten part should be continued for another 48 hr.
  - Children require more antivenom; ↑ dose by 50%.
  - Pregnancy is not a contraindication to antivenom.
  - Immunize against tetanus if no booster within past 5 yr; if never immunized, give immunoglobulin as well as toxoid.
  - Manage pain as needed (acetaminophen, codeine, meperidine).
  - Avoid sedation in Mojave rattlesnake, eastern diamondback rattlesnake, and coral snake bites.
  - Abx reserved for moderate to severe cases; use those w/broad-spectrum coverage (which includes gram-negatives, i.e., quinolone derivatives).
- Most frequent complication of treated envenomations is serum sickness; occurs 7-14 days after antivenom administration and is characterized by fever, rash, arthralgias, and lymphadenopathy. It can be treated w/PO prednisone 60 mg/day, tapered during 7-10 days. Acutely, there is the risk of anaphylaxis to antivenin as mentioned previously. This occurs within 30 min and is treated with
  - IV epinephrine
  - IV diphenhydramine
  - IV hydrocortisone
- Injuries also result from
  - Tourniquet placement
  - Cryotherapy
- National poison control hotline: 800-222-1222

78 BOTULISM

Definition
Illness caused by a neurotoxin produced by *Clostridium botulinum*. Three types of disease can occur: food-borne botulism, wound botulism, and infant intestinal botulism. Recent concern has ↑ about a possible fourth type of disease, inhalational botulism, which does not occur naturally but may occur as a result of bioterrorism.

Diagnosis

H&P
- Sx usually begin 12-36 hr after ingestion.
- Severity of illness is related to the quantity of toxin ingested.
Significant findings:
- Cranial nerve palsies, w/ocular and bulbar manifestations being most frequent (diplopia, ophthalmoplegia, ptosis, dysphagia, dysarthria, fixed and dilated pupils, and dry mouth)
- Usually bilateral nerve involvement that may progress to a descending flaccid paralysis
- Typically, absence of sensory findings; sensorium intact
- GI sx (N/V, diarrhea, or cramps)
- Usually no fever

**Wound botulism**
- Occurs mostly in injecting drug users (SC heroin injection—“skin popping”) or w/traumatic injury
- Presentation is similar to that of food-borne disease, except for a longer incubation period and the absence of GI sx.
- Wound infection is not always apparent, but injection sites frequently reveal cellulitis, draining pus, or abscess formation.

**Labs**
- Samples of food and stool are cultured for the organism.
- Food, serum, and stool are sent for toxin assay.

**Etiology**
- Cause is one of several types of neurotoxins (usually A, B, or E) produced by *C. botulinum*, an anaerobic, gram-positive bacillus. Spore production guarantees survival of the organism in extreme conditions. Botulinum toxin is the most powerful neurotoxin known.
- Disease results from absorption of toxin into the circulation from a mucosal surface or wound. Botulinum toxin does not penetrate intact skin.
- In food-borne variety, disease is caused by ingestion of preformed toxin. Although rapidly inactivated by heat, the toxin can survive the proteolytic environment of the stomach.
- In wound botulism, toxin is elaborated by organisms that contaminate a wound. Most cases reported are from California.
- In infant botulism, toxin is produced by organisms in the GI tract. Avoid giving honey to infants as there is ↑ risk of infant botulism.
- Inhalational botulism has been demonstrated experimentally in primates. This manufactured form results from aerosolized toxin and has been attempted by bioterrorists.

**Treatment**
- Give trivalent equine serum botulinum antitoxin as early as possible. Once a clinical dx is made, antitoxin should be administered before laboratory confirmation.
- Give one vial by IM injection and one vial IV.
- The antitoxin is available from the Centers for Disease Control and Prevention (404-639-2206 or 404-639-2888); it is derived from horse serum, so there is a significant incidence of serum sickness. A human-derived antitoxin immunoglobulin is now available for infants <1 yr of age (BIG-IV).
- Skin testing (conjunctival instillation and observation for 15 min), and possible desensitization, is recommended before treatment.
- Give wound botulism pts PCN 2 million U IV q4h.
- Babies w/infantile intestinal botulism may benefit from a cathartic to mechanically clear the number of *C. botulinum* vegetative forms and spores residing in the GI tract.

**Clinical Pearls**
- Routine cooking inactivates the toxin, but spores are resistant to environmental factors. At room temperature, spores can germinate and produce toxin.
- Most outbreaks are associated w/home-canned foods, especially vegetables.
- Pts must be closely monitored for progression to respiratory paralysis.
- There is ↑ concern about the potential use of botulinum toxin as a biologic weapon, either by the enteric route or by aerosolization.
Notify public health authorities immediately to alert other health care services of possible additional cases and to initiate investigation into cause and scope of outbreak.

Recent botulism food recalls have involved canned chili, cut green beans, and olives.

75 BREAST CANCER

Definition
Malignant neoplasm involving breast tissue. A number of pathologic classifications of breast carcinoma are used, with some presented by the Armed Forces Institute of Pathology and the WHO the most common. Breast tumors usually originate from breast epithelium and are either ductal or lobular, corresponding to the ducts and lobules of the nl breast. Eighty percent of malignant neoplasms are infiltrating ductal carcinomas; less common are infiltrating lobular carcinoma, medullary carcinoma, and mucinous carcinoma. Pts w/medullary and mucinous carcinomas have a better survival rate than do those w/infiltrating ductal carcinoma. Inflammatory breast cancer is characterized by skin edema and an erythematous margin w/induration of the surrounding tissue. On microscopic examination, this is associated w/involvement of dermal lymphatics by tumor and carries a poor prognosis. Ductal carcinoma in situ (DCIS) represents carcinoma confined to the preexisting ductal system of the breast w/o evidence of penetration of the basement membrane by light microscopy. Ductal carcinoma in situ accounts for 10%-15% of all breast cancers.

Diagnosis

H&P
- Most breast cancers (90%) are discovered first by the woman herself or her sexual partner.
- Up to 10% of breast cancers may be clinically evident while mammographically occult.
- Malignant breast masses are usually fixed nontender and firm w/irregular borders. Approximately 50% of all breast cancers develop in the upper outer quadrant of the breast.
- Changes in contour, swelling, any dimpling or puckering of the skin, or a change in the nipple is of concern.
- Dx is established only by bx.

Staging (Table 3-6)
- Staging workup includes H&P, CXR, CBC, and liver chemistries. The value of bone scan, liver scan, and PET scan has been a matter of controversy. Several tumor markers, including the carcinoembryonic antigen (CEA), CA 15-3, and CA 27.29. may be valuable in determining treatment response and recurrent disease. Sentinel lymph node evaluation is used as part of staging of invasive breast cancer. If the sentinel lymph node is negative for tumor, the axillary node dissection is not performed.

Labs
- All breast cancers should be tested for estrogen receptor (ER) and progesterone receptor (PR) proteins. ER-positive tumors are usually less virulent and more likely to respond to hormonal manipulation (drugRx or surgery). Tumors that contain both ERs and PRs have the greatest likelihood of responding to endocrine Rx, and the probability of a response ↑ directly w/iter of the receptor protein. The human epidermal growth factor receptor 2 (Her-2) is detectable in approximately 20%-30% of breast cancers, and it is now frequently measured in tumor samples from pts w/newly diagnosed breast cancer. Her-2 is used as a prognostic indicator and may also be predictive of poor response to Rx.
- Fluorescent in situ hybridization (FISH): permits the detection of numerous chromosomal alterations in tissue sections or cytologic preparations.

Imaging
- Mammography, breast ultrasound
- MRI of the breast has a sensitivity of between 90% and 100%.

Treatment
The ideal treatment of early breast cancer still generates controversy among physicians and pts, w/factors such as pt age, cancer stage and prognosis, ER
status, type of surgery, role of radiation Rx, need and type of chemotherapy, hormonal Rx, and length of treatment all contributing to the decision-making process. Some treatment recommendations include the following:

- Localized DCIS: lumpectomy followed by radiation and tamoxifen
- Stages I and II: premenopausal (ER negative)
  - Tumor size <1 cm: lumpectomy and local radiation
  - Tumor size ≥1 cm: lumpectomy w/axillary dissection, six cycles of chemotherapy followed by radiation
- Stage I: premenopausal (ER positive)
  - Tumor size <1 cm: lumpectomy, local radiation Rx, and hormonal Rx
  - Tumor size ≥1 cm: lumpectomy, six cycles of chemotherapy w/radiation and hormonal Rx
- Stage II: premenopausal (ER negative): lumpectomy w/dissection and six cycles of chemotherapy and radiation
- Stages I and II: postmenopausal (ER negative)
  - Modified radical mastectomy and 6 mo of adjuvant chemotherapy, or
  - Lumpectomy w/axillary dissection, six cycles of adjuvant chemotherapy, and local radiation
- Stages I and II: postmenopausal (ER positive)
  - Lumpectomy w/axillary dissection, local radiation Rx, and hormonal Rx, or
  - Lumpectomy w/axillary dissection, local radiation, and aromatase inhibitor Rx
- Stage III (locally advanced breast cancer)
  - Induction chemotherapy followed by modified radical mastectomy followed by 1-2 additional years of chemotherapy, or
  - Induction chemotherapy followed by primary radiation followed by 1-2 additional years of chemotherapy
- Stage IV disease: systemic chemotherapy, hormonal Rx, or both, depending on multiple factors
- The main chemotherapeutic agents used are cyclophosphamide, MTX, and 5-FU (CMF) or doxorubicin substituted for MTX (CAF); other useful drugs

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**TABLE 3-6** Staging of Breast Cancer: The TNM

<table>
<thead>
<tr>
<th>Tumor Size—T (Largest Diameter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget’s disease of the nipple with no tumor</td>
</tr>
<tr>
<td>T1 Tumor ≤2 cm in greatest dimension</td>
</tr>
<tr>
<td>T2 Tumor &gt;2 cm but not &gt;5 in greatest dimension</td>
</tr>
<tr>
<td>T3 Tumor &gt;5 cm in greatest dimension</td>
</tr>
<tr>
<td>T4 Tumor of any size with direct extension to chest wall* or skin (includes inflammatory carcinoma)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal Involvement—N (Nodal Status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX Regional lymph nodes cannot be assessed (e.g., previously removed, not removed)</td>
</tr>
<tr>
<td>N0 No regional lymph node metastases histologically</td>
</tr>
<tr>
<td>N1 Metastasis to one to three ipsilateral axillary nodes</td>
</tr>
<tr>
<td>N2 Metastases to four to nine ipsilateral axillary nodes or internal mammary lymph nodes in absence of axillary lymph node metastasis</td>
</tr>
<tr>
<td>N3 Metastases to 10 or more ipsilateral internal mammary lymph nodes, or to internal mammary lymph nodes and axillary lymph nodes, to ipsilateral supraclavicular lymph nodes, or to ipsilateral infraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

**Metastases—M**

| M0 No evidence of distant metastases |
| M1 Distant metastases |

*The chest wall includes the ribs, intercostal muscles, and serratus anterior but not the pectoral muscle.*
include paclitaxel, docetaxel, vinorelbine, vincristine, vinblastine, mitomycin C, thiotepa, gemcitabine, and cisplatin. Trastuzumab, a monoclonal Ab targeting the extracellular domain of the HER2 protein, when combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women w/surgically removed HER2-positive breast cancer.

- Ovarian suppression plus tamoxifen is a standard adjuvant treatment in premenopausal women w/endocrine-responsive breast cancer.
- The addition of zoledronic acid to adjuvant endocrine Rx improves disease-free survival in premenopausal pts w/estrogen-responsive early breast cancer.
- High-dose chemotherapy (HDCT) and autologous bone marrow transplantation in selected pts have produced complete remission rates; duration of the response has not yet been convincingly demonstrated as prolonged, and the median follow-up time is still short. Studies have failed to show any significant benefits of bone marrow transplantation over chemotherapy alone.
- Bisphosphonates in monthly infusions may ↓ the complications and morbidity of skeletal mets.
- The use of trastuzumab in pts whose tumor overexpresses the HER2 protein has a significant role in treatment of pts w/HER2-positive disease. It should, however, not be used concurrently w/anthracyclines because of an ↑ risk of cardiac toxicity (↑ risk of CHF).
- Aromatase inhibitors are superior to tamoxifen in postmenopausal pts. Aromatase inhibitors (anastrozole and letrozole) have also been shown to be useful in metastatic breast cancer. They function by blocking estrogen synthesis in ER-positive tumors. The aromatase inhibitor letrozole has also been reported to be more effective treatment of metastatic breast cancer and more effective in the neoadjuvant setting than tamoxifen. Use of raloxifene is associated with the reduction of the risk of invasive breast cancer in postmenopausal women.
- The prophylactic use of tamoxifen may ↓ the risk for development of breast cancer by 50%. For postmenopausal women w/hormonally responsive tumor, use of an aromatase inhibitor or switching to an aromatase inhibitor after 2–3 yr of tamoxifen use improves disease-free survival compared w/5 yr of tamoxifen use.
- Prophylactic bilateral mastectomy ↓ the risk of breast cancer development by approximately 90% and oophorectomy ↓ the risk of breast cancer by 50% if performed before menopause in high-risk women (those carrying BRCA mutations).

**Prognosis**

- See Table 3-7

### TABLE 3-7 TNM Stage and Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Category</th>
<th>Recurrence Free at 10 Years (No Systemic Adjuvant Therapy), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
<td>98</td>
</tr>
<tr>
<td>I</td>
<td>T1, N0, M0</td>
<td>80 (all stage I patients)</td>
</tr>
<tr>
<td></td>
<td>T &lt;1 cm</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>T &gt;1-2 cm</td>
<td>80-90</td>
</tr>
<tr>
<td>II A</td>
<td>T0, N1, M0; T2, N0, M0</td>
<td>60-80</td>
</tr>
<tr>
<td></td>
<td>T1, N1, M0</td>
<td>50-60</td>
</tr>
<tr>
<td>II B</td>
<td>T2, N1, M0</td>
<td>5-10; worse than II A and based on node status</td>
</tr>
<tr>
<td></td>
<td>T3, N0, M0</td>
<td>30-50</td>
</tr>
<tr>
<td>III A</td>
<td>T0 or T1 or T2, N2, M0; or T3, N1 or N2, M0</td>
<td>10-60</td>
</tr>
<tr>
<td>III B</td>
<td>T4, N0 or N1 or N2, M0</td>
<td>5-30</td>
</tr>
<tr>
<td>III C</td>
<td>Any T, N3, M0</td>
<td>15-20</td>
</tr>
<tr>
<td>IV</td>
<td>Any T, any N, M1</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
30 BRONCHIECTASIS

Definition
Abnormal dilation and destruction of bronchial walls, which may be congenital or acquired.

Diagnosis
H&P
- Clinical presentation: cough with expectoration of large amount of purulent sputum, fever, night sweats, generalized malaise, weight loss, hemoptysis
- PE: moist crackles at lung bases, halitosis, skin pallor

Imaging
- CXR: hyperinflation, crowded lung markings, small cystic spaces at the base of the lungs
- High-resolution CT of the chest: best tool to detect cystic lesions and to exclude underlying obstruction from neoplasm

Etiology
- Cystic fibrosis
- Lung infections (pneumonia, lung abscess, TB, fungal infections, viral infections)
- Abnormal host defense (panhypogammaglobulinemia, Kartagener’s syndrome, AIDS, chemotherapy)
- Localized airway obstruction (congenital structural defects, foreign bodies, neoplasms)
- Inflammation (inflammatory pneumonitis, granulomatous lung disease, allergic aspergillosis)

Treatment
- Postural drainage (reclining prone on a bed with the head down on the side) and chest percussion with use of inflatable vests or mechanical vibrators applied to the chest may enhance removal of respiratory secretions.
- Adequate hydration
- Supplemental O₂ for hypoxemia
- Abx Rx: based on the results of sputum, Gram stain, and C&S; in pts with inadequate or inconclusive results, empiric Rx with amoxicillin-clavulanate 500-875 mg q12h, TMP-SMX q12h, doxycycline 100 mg bid, or cefuroxime 250 mg bid for 10-14 days is recommended.
- Bronchodilators: useful in pts with demonstrable airflow obstruction.

Clinical Pearl
- Surgical referral for partial lung resection should be considered in pts with localized severe disease unresponsive to medical Rx or in pts with massive hemoptysis.

31 BRUGADA SYNDROME

Definition
Repetational disorder occurring in structurally normal heart characterized by:
- ST segment elevation in right anterior precordial leads (V₁ to V₃)
- Incomplete RBBB
- Susceptibility to ventricular tachyarrhythmias

Diagnosis
- Manifested usually in third-fourth decade with cardiac events (syncope, cardiac arrest), often occurring during sleep or at rest
- Male:female ratio is 8:1.
- Role of PES to identify pts at higher risk of cardiac arrest is controversial.

Etiology
- Autosomal dominant. Mutation of SCN5A gene results in loss of sodium channel function.

Treatment
- ICD to prevent cardiac arrest

Clinical Pearl
- Concealed forms may be unmasked only by provocative drug testing with selected class IC drugs (flecainide, procainamide).
**32 BUDD-CHIARI SYNDROME (BCS)**

**Definition**
Disease defined by the obstruction of hepatic venous outflow anywhere from the small hepatic veins to the junction of the IVC and the right atrium. Primary BCS is defined by endoluminal obstruction as seen in thrombeses or webs. In secondary BCS, the obstruction is due to nonvascular invasion (malignant neoplasm or parasitic masses) or extrinsic compression (tumor, abscess, cysts).

**Diagnosis**

**H&P**
- Variable according to the degree, location, and acuity of obstruction and presence of collateral circulation
- Fulminant/acute (uncommon): severe RUQ abd pain, fever, N/V, jaundice, hepatomegaly, ascites, marked ↑ in serum aminotransferases and ↓ in coagulation factors, and encephalopathy. Early recognition and treatment are essential to survival.
- Subacute/chronic (more common): vague abd discomfort, gradual progression to hepatomegaly, portal HTN w/ or w/o cirrhosis; late-onset ascites, LE edema, esophageal varices, splenomegaly, coagulopathy, HRS, and, rarely, encephalopathy
- Asymptomatic: usually discovered incidentally

**Imaging**
- Color and pulsed Doppler U/S: diagnostic sensitivity of >85%, first-line test
- MRI w/gadolinium contrast: better than contrast-enhanced CT, second-line test
- Venography: gold standard but invasive and mainly indicated to guide percutaneous or surgical intervention, to confirm the classic “spider web” pattern caused by collateral venous flow, to look for BCS in cases of high clinical suspicion when initial studies are normal

**Etiology**
- Myeloproliferative disease
- Hypercoagulable states: can coexist w/other causes, up to 31%
- Infection
- Malignant disease: <5%
- Other: sarcoid, Behçet’s disease, PNH, abd trauma, UC, celiac disease, dacarbazine Rx, idiopathic

**Treatment**
- Anticoagulation, first w/LMWH, followed by coumadin, even in the absence of an underlying hypercoagulable disorder
- In situ thrombolysis
- Balloon angioplasty: complicated by 50% restenosis rate
- Stenting: may improve long-term patency rates to 90%; but if placed above the intrahepatic IVC, may complicate future liver transplantation
- TIPS has been used successfully in the emergent setting of fulminant hepatic failure and is growing in use despite 50% long-term patency rates.
- Surgical portal systemic shunts: may be difficult to find a surgeon experienced enough to perform these.
- Liver transplantation may be indicated for pts who fail the previous therapies or have advanced liver dysfunction.
- Lifelong anticoagulation; warfarin Rx w/target INR 2-3; lessens but does not completely prevent recurrence
- Treatment of underlying myeloproliferative or other disorders
- Treatment of liver dysfunction and complications related to portal HTN, such as ascites
- Invasive interventions should be reserved for symptomatic pts who do not improve w/medical Rx.

**33 BULIMIA NERVOSA**

**Definition**
DSM-IV criteria:
- Recurrent episodes of binge eating (rapid consumption of a large amount of food in a discrete period of time)
A feeling of lack of control over eating behavior during the eating binges
Self-induced vomiting, use of laxatives or diuretics, strict dieting or fasting, or rigorous exercise to prevent weight gain
≥2 binge-eating episodes a week for ≥3 mo
Persistent overconcern w/body shape and weight

**Diagnosis**

**H&P**

- The following questions are useful to screen pts for bulimia:
  - Are you satisfied w/your eating habits?
  - Do you ever eat in secret?
- Answering no to the first question or yes to the second question has 100% sensitivity and 90% specificity for bulimia. The SCOFF questionnaire can also be used as a screening tool for eating disorders (see *Anorexia Nervosa*).
- Parotid and salivary gland swelling
- Scars on the back of the hand and knuckles (*Russell’s sign*) from rubbing against the upper incisors when inducing vomiting
- Eroded enamel, particularly on the lingual surface of the upper teeth; pyorrhea and other gum disorders possible
- Petechial hemorrhages of the cornea, soft palate, or face possibly noted after vomiting
- Loss of gag reflex, well-developed abd musculature
- Body weight may be low or normal.

**Labs**

- Electrolyte abnormalities secondary to vomiting (↓ K⁺, metabolic alkalosis) or to diarrhea from laxative abuse (↓ K⁺, hyperchloremic metabolic acidosis)
- ↓ Na, Ca, Mg (caused by laxative abuse)
- ↑ Cortisol, ↓ LH, FSH

**Etiology**

- Likely multifactorial (sociocultural, psychological, familial factors). Bulimia is much more common in Western societies where there is a strong cultural pressure to be slender.

**Treatment**

- Cognitive-behavioral therapy to control abnl behaviors
- Use of food diaries, nutritional counseling, and planning meals at least a day in advance are useful to counter abnl eating behaviors.
- Correction of electrolyte abnormalities
- SSRIs are generally considered to be the safest medication option in these pts. They are useful in severely depressed pts and in those who fail to benefit from cognitive-behavioral Rx.

**Clinical Pearl**

- Bulimia has a close association w/depression, bipolar disorder, obsessive-compulsive disorder, alcoholism, and substance abuse.

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**BULLOUS PEMPHIGOID**

**Definition**

Autoimmune, subepidermal blistering disease.

**Diagnosis**

**H&P**

- Typically starts as an eczematous or urticarial rash on the extremities
- Blisters form between 1 wk and several months
- Anatomic distribution of lesions:
  - Flexor surfaces of the arms, legs, groin, axilla, and lower abd
  - Spares the head and neck
  - Rare involvement of mucous membranes
- Lesion configuration:
  - May be localized to the extremities or generalized
  - Lesions irregularly grouped but sometimes can be serpiginous
Diseases

The extent thermal injuries (burns) include area (TBSA). Total burns as cigarettes or bombs of best scalds, burns.

**Lesion morphology:**
- Blistering bullae are characteristic findings, measuring anywhere from 5 mm to 2 cm in diameter
- Contains clear or bloody fluid
- Arises from nl skin or from an erythematous base
- Heals w/o scarring if denuded

**Labs**
- Ab to the basement membrane zone in the serum in 70% of pts w/bullous pemphigoid
- Skin bx staining w/hematoxylin and eosin reveals subepidermal blisters.
- Direct and indirect immunofluorescence studies to detect the presence of IgG and C3 immune complexes
- Immunoelectron microscopy also reveals immune deposits on the basement membrane zone.
- Skin bx is required to make the dx.

**Etiology**
- Autoimmune disease w/IgG or C3 complement components reacting w/ antigens located in the epidermal basement membrane zone
- Drug-induced pemphigoid, although rare, can occur in pts taking penicillamine, furosemide, captopril, PCN, and sulfasalazine.

**Treatment**
- Systemic disease: prednisone, alone or in combination w/a steroid-sparing agent such as azathioprine, mycophenolate mofetil, or a tetracycline. They can be started simultaneously, followed by a gradual tapering of the prednisone and continuation of the steroid-sparing agent until clinical remission is achieved. A min. dose of prednisone of 1 mg/kg/day is usually recommended and is continued until new blister formation ceases. The dose is gradually tapered according to the clinical findings.
- Localized disease: topical steroids in general have been used in localized bullous pemphigoid. Clobetasol 40 g/day divided in bid application is continued until 15 days after disease containment, at which time the dose is tapered to 20 g/day × 1 mo, 10 g/day × 2 mo, followed by 10 g every other day × 4 mo, and then 10 g twice weekly × 4 mo.
- MTX may be used in pts w/severe disease who are unable to tolerate prednisone.

**Clinical Pearls**
- Bullous pemphigoid has been associated w/diabetes, MS, pernicious anemia, RA, lichen planus, psoriasis, and vitiligo.
- It is not known to transform into malignant neoplasms or to represent a dermatologic manifestation of harboring malignant neoplasms.

**BURNS**

**Definition**
Burn injuries include thermal injuries (flames, scalds, cigarettes) as well as chemical, electrical, and radiation burns. Burns are classified on the basis of the extent of the burn or total burn surface area (TBSA). The TBSA is best classified by use of age-specific burn charts.

- **Major burns:** partial-thickness burns >25% TBSA (or 20% if younger than 10 or older than 50 yr); full-thickness burns >10% TBSA; burns crossing major joints or involving the hands, face, feet, or perineum; electrical or chemical burns; those complicated by inhalation injury or involving high-risk pts (extremes of age/comorbid diseases)
- **Moderate burns:** partial-thickness burns >15%-25% TBSA (or 10% in children and older adults); full-thickness burns >2%-10% TBSA and not involving the specific conditions of major burns
- **Minor burns:** partial-thickness burns <15% TBSA or full-thickness burns <2% TBSA

**Diagnosis**

**H&P**
- Burns are defined on the basis of the surface area and depth of skin involved: “rule of nines” (Fig. 3-16).
First-degree burns (superficial) involve the epidermis only and appear painful and red.

Second-degree burns involve the dermis and appear blistered, moist, and red with two-point discrimination intact (superficial partial thickness) or red and blanched white with only sensation of pressure intact (deep partial thickness).

Third-degree burns (full thickness) extend through the dermis with associated destruction of hair follicles and sweat glands. The skin is charred, pale, painless, and leathery. These burns are caused by flames, immersion scalds, chemical and high-voltage injuries.

**Labs**
- CBC, lytes, BUN, Cr, and glucose
- Serial ABG and carboxyhemoglobin if smoke inhalation suspected
- U/A, urine myoglobin, and CPK levels if concern for rhabdo

**Imaging**
- CXR if smoke inhalation suspected

**Treatment**

**Acute General Rx**
- Establish airway: inspect for inhalation injury and intubate for suspected airway edema (often seen 12-24 hr later); supplemental O₂.
- Remove jewelry and clothing and place one or two large-bore peripheral IVs (if TBSA >20%).
- Fluid resuscitation w/lactated Ringer’s solution at 2-4 mL/kg per % TBSA per 24 hr w/half the calculated fluid given in the first 8 hr
- Foley catheter and NG tube (20% of pts develop an ileus)
- Tetanus update
- Pain control
- Stress ulcer prophylaxis in high-risk pts
- Address adequate nutritional support.
- Prophylactic abx are not recommended; however, burn victims should be considered immunosuppressed.
- High-voltage burn pts should have ECG monitoring because they are at ↑ risk for arrythmias.

**Figure 3-16.** The “rule of nines” for estimating second-degree and third-degree burns. Because infants have significantly larger heads and smaller legs than adults do, different rules must be used in evaluating these patients. A simple, practical rule is that the palm of the patient’s hand, with fingers, equals 1% of the total body surface area.
Burn Wound Rx

- **First-degree burns** (e.g., sunburns) can be Rx w/cool compresses, antihistamines, emollients, and, at times, a rapidly tapering dose of steroids.
- **Second-degree and third-degree burns:**
  - Wash burned skin w/cool tap water or saline (15°C-25°C; immerse approximately 30 min if able) and cleanse w/mild soap. Ice or ice water may ↑ tissue injury and should not be used.
  - Sharp débridement of ruptured blisters (except palms and soles). Leave unruptured blisters intact.
- There are several approaches to burn dressings after cleansing and débridering:
  - Apply thin layer of abx ointment (silver sulfadiazine can be used unless sulfa allergy or facial burn) and cover w/nonadherent dressing (e.g., Telfa or petroleum-soaked gauze) followed by a sterile gauze wrap. Wash wound and change dressing when dressing is soaked.
  - Apply saline-soaked gauze (Xeroform, Owen’s), cover w/4 × 4 dressing and a bulky absorbent dressing such as Kerlix. Re-evaluate in 5–7 days.
  - Apply occlusive dressing (DuoDERM, Tegasorb); remove in 7-10 days.
- Specialized care, such as excision and autografting, is required for some deep second-degree and most third-degree burns.

86 CANDIDIASIS

**Definition**
Superficial mycotic infection of the skin usually caused by the yeast *Candida albicans*.

**Diagnosis**

**H&P**
- The affected area has a red glistening surface w/an advancing border and cigarette paper–like scaling.
- The intertriginous skin folds, such as inner thighs, or other moist, occluded sites, such as underneath the breasts, are most frequently affected.
- Factors that predispose to infection include DM, obesity, increasing moisture, use of systemic corticosteroids or abx, and immunocompromised status.

**Labs**
- Presence of branching pseudohyphae and budding yeast forms on potassium hydroxide preparation (KOH) or other stains confirms the dx.
- Serum glucose, HIV serology (in recurrent cases)

**Treatment**
- Affected skin sites that are moist should be dried out w/wet-to-dry soaks and exposed to air.
- Topical antifungal products (miconazole, clotrimazole, econazole) are generally effective.
- Oral Rx (fluconazole, itraconazole) is reserved for resistant cases.

87 CARBON MONOXIDE POISONING

**Definition**
CO is a colorless, odorless, tasteless, nonirritating gas. When inhaled, it produces toxicity by causing cellular hypoxia.

**Diagnosis**

**H&P**
- Presentation is often nonspecific.
- Mild to moderately severe poisoning may present w/headache, fatigue, dizziness, nausea, dyspnea, confusion, or blurry vision.
- Severe poisoning may present w/arrhythmias, myocardial ischemia, pulmonary edema, lethargy, ataxia, syncope, seizure, coma, or cherry-red skin.

**Labs**
- Carboxyhemoglobin level (COHgb). Note: COHgb level >5% in nonsmoker confirms exposure. Heavy smokers may have levels of 10%.
Diseases and Disorders

- Direct measurement of arterial oxygen saturation. Note: Pulse oximetry and ABG may be falsely nd because neither measures oxygen saturation directly. Pulse oximetry is inaccurate because of the similar absorption characteristics of oxyhemoglobin and carboxyhemoglobin. An ABG is inaccurate because it measures oxygen dissolved in plasma (which is not affected by CO) and then calculates oxygen saturation.
- Lytes, glucose, BUN, Cr, CPK, ABG (because lactic acidosis and rhabdo may develop)
- Pregnancy test (fetus at high risk)
- Consider toxicology screen

**Imaging**
- CXR
- ECG (r/o ischemia)

**Etiology**
- CO poisoning occurs when individuals are exposed to smoke from fires; motor vehicle exhaust; or the burning of wood, charcoal, or natural gas for cooking or heating in poorly ventilated areas.

**Treatment**
- Remove from site of CO exposure.
- Ensure adequate airway.
- Continuous ECG monitor
- Fetal monitoring if pregnant
- 100% oxygen by tight-fitting non-rebreather mask or ETT for 6-12 hr (↓ half-life of COHgb from 4-6 hr to 60-90 min)
- Hyperbaric oxygen (2.5-3 atm)
  - ↓ Half-life of COHgb to 20-30 min, ↑ amount of oxygen dissolved in plasma
  - Questionable if there is any beneficial effect over normobaric oxygen
  - May prevent the delayed neurologic sequelae of CO poisoning by ↓ cellular hypoxia and toxicity
  - Consider for individuals with
    - Severe intoxication (COHgb >25%, h/o loss of consciousness, neurologic sx or signs, CV compromise, severe metabolic acidosis)
    - Persistent sx after 2-4 hr of normobaric oxygen
    - Pregnant women w/COHgb >15% or signs of fetal distress: CO elimination slower in fetus than in mother; fetal Hgb has greater affinity for CO than adult Hgb does
  - Should be instituted quickly if deemed necessary
  - Consider concomitant poisoning w/other toxic/irritant gases that may be present in smoke (e.g., cyanide) or thermal injury to airway. Toxic effects of CO and cyanide are synergistic.
  - Identify source of exposure and determine if poisoning was accidental.

**Clinical Pearls**
- Survivors of severe poisoning are at 14%-40% risk for neurologic sequela ranging from parkinsonism to neuropsychiatric sx (personality and memory disorders). Neurologic deficits are usually apparent within 3 wk of poisoning (but may present months later). Brain MRI may show changes in the white matter and basal ganglia.
- Sx of toxicity and prognosis do not correlate well w/carboxyhemoglobin levels.

**Carcinoid Syndrome**

**Definition**
Sx complex characterized by paroxysmal vasomotor disturbances, diarrhea, and bronchospasm caused by the action of amines and peptides (serotonin, bradykinin, histamine) produced by tumors arising from neuroendocrine cells.

**Diagnosis**

**H&P**
- Cutaneous flushing (75%-90%)
- The pt usually has red-purple flushes starting in the face, then spreading to the neck and upper trunk.
The flushing episodes last from a few minutes to hours (longer lasting flushes may be associated w/bronchial carcinoids).
Flushing may be triggered by emotion, alcohol, or foods, or it may occur spontaneously.
Dizziness, tachycardia, and hypotension may be associated w/the cutaneous flushing.
Diarrhea (>70%): often associated w/abd bloating and audible peristaltic rushes
Intermittent bronchospasm (25%): characterized by severe dyspnea and wheezing
Facial telangiectasia
Tricuspid insufficiency, pulmonic stenosis from carcinoid heart lesions

**Labs**

The biochemical marker for carcinoid syndrome is ↑ 24-hr urinary 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin (5-hydroxytryptamine). False ↑ can be seen w/ingestion of certain foods (bananas, pineapples, eggplant, plums, tomato products, kiwi fruit, avocados, walnuts) and certain medications (acetaminophen, antihistamines, caffeine, antipsychotics, nicotine, muscle relaxants, warfarin, guaifenesin, reserpine). Others, such as alcohol, ASA, MAOIs, and St. John’s wort, can cause falsely ↓ results; therefore, pts should be on a restricted diet and should avoid these medications when the test is ordered.
Biochemical screening can also be done w/plasma chromogranin A. Many endocrinologists prefer this test for initial screening because of its high sensitivity (75%), but it is not very specific (can be ↑ w/CHF, renal failure, PPI, HTN, chronic atrophic gastritis).

**Imaging**

CXR: to detect bronchial carcinoids
CT of abd or a liver/spleen radionuclide scan: useful to detect liver mets (palpable in >50% of cases)
Somatostatin receptor scintigraphy: preferred imaging test. Iodine 123–labeled somatostatin (123I-SS) can detect carcinoid endocrine tumors w/somatostatin receptors.

**Etiology**

Neoplasms originating from neuroendocrine cells
Carcinoid tumors are principally found in the following organs: appendix (40%); small bowel (20%; 15% in the ileum); rectum (15%); bronchi (12%); esophagus, stomach, colon (10%); ovary, biliary tract, pancreas (3%).

**Treatment**

Surgical resection
Somatostatin analogues: octreotide or lanreotide can control flushing and diarrhea in 70%-80% of pts.
Interferon alpha: may be used as an additive Rx when sx persist.
Percutaneous embolization and ligation of the hepatic artery: can ↓ the bulk of the tumor in the liver and provide palliative treatment of tumors w/hepatic mets.
Cytotoxic chemotherapy: combination chemotherapy w/5-FU and streptozocin can be used in pts w/unresectable or recurrent carcinoid tumors; however, it has only limited success.
Bronchodilators for bronchospasm
Nutritional support: supplemental niacin Rx may be useful to prevent pellagra because the tumor uses dietary tryptophan for serotonin synthesis, resulting in a nutritional deficiency in some pts.
SC somatostatin analogues (octreotide 150 µg SC tid): for long-term control of sx in pts w/unresectable neoplasms

**Clinical Pearls**

Echo and monitoring for right-sided CHF are recommended for pts w/unresectable disease because endocardial fibrosis, involving predominantly the endocardium, chordae, and valves of the right side of the heart, can occur and result in right-sided CHF.
Carcinoids of the appendix and rectum have a low malignancy potential and rarely produce the clinical syndrome; mets are also uncommon if the size of the primary lesion is <2 cm in diameter.

Carcinoid tumors do not usually produce the syndrome unless liver mets are present or the primary tumor does not involve the GI tract.

89 CARDIAC RISK ASSESSMENT FOR NONCARDIAC SURGERY

Risk of Major Perioperative Cardiovascular Event by Type of Surgery

- High risk (death or MI >4%): thoracic, vascular
- Intermediate risk (2%-4%): abd, head and neck
- Low risk (≤1%): breast, eye, gyn, skin, urologic

Clinical Risk Stratification: Risk of MI

- High (4.1%): CAD almost certain (MI by hx/ECG; typical angina; prior angiography or revascularization)
- Intermediate (0.8%): PVD, prior stroke/TIA, atypical chest pain but no evidence of CAD
- Low (<0.8%): risk factors for CAD but no obvious disease, age >75 yr, ECG abnl

Simplified Approach

- No h/o sx of CAD, fully active → no additional recommended tests
- High likelihood of CAD, stable CAD functional class I, II → cardiac stress testing
- Unstable CAD functional class III or IV → cardiac catheterization

90 CARDIAC TAMponade

Definition

Pericardial effusion that significantly impairs diastolic filling of the heart.

Diagnosis

H&P

- Dyspnea, orthopnea, interscapular pain
- PE: Beck’s triad: distended neck veins, distant heart sounds and hypotension. Other manifestations include: ↓ apical impulse, diaphoresis, tachypnea, tachycardia, Ewart’s sign (an area of dullness at the angle of the left scapula caused by compression of the lungs by the pericardial effusion), pulsus paradoxus (↓ in systolic BP >10 mm Hg during inspiration), hypotension, narrowed pulse pressure

Imaging

- Echo: detects effusions as small as 30 mL; a paradoxical wall motion may also be seen.
- CXR: cardiomegaly (water bottle configuration of the cardiac silhouette may be seen) w/clear lungs; CXR may be nl when acute tamponade occurs rapidly in the absence of prior pericardial effusion.
- Cardiac cath: equalization of pressures within chambers of the heart, ↑ of RAP w/prominent x but no significant y descent
- MRI can also be used to dx pericardial effusions.
- ECG: ↓ amplitude of the QRS complex, variation of the R wave amplitude from beat to beat (electrical alternans). This results from the heart oscillating in the pericardial sac from beat to beat and frequently occurs w/neoplastic effusions.

Treatment

- Immediate pericardiocentesis, preferably by needle paracentesis w/the use of echo, fluoroscopy, or CT; in pts w/recurrent effusions (e.g., neoplasms), placement of a percutaneous drainage catheter or pericardial window draining in the pleural cavity may be necessary. Aspirated fluid should be sent for analysis (protein, LDH, cytology, CBC, Gram stain, AFB stain) and cultures for AFB, fungi, and bacterial C&S.

Clinical Pearls

- Cardiac tamponade should always be considered in pulseless electrical activity arrest and may require subxiphoid pericardiocentesis.
Evaluation for pulsus paradoxus should always be performed during nl respiration because deep inspiration will elevate the difference.

As little as 200 mL of fluid can lead to acute cardiac tamponade; whereas w/gradual accumulation, the pericardial sac can hold >1 L of fluid before tamponade occurs.

91 CARDIOMYOPATHY, ARRHYTHMOGENIC RIGHT VENTRICULAR

Definition
Cardiomyopathies are a group of diseases primarily involving the myocardium and characterized by myocardial dysfunction that is not the result of HTN, CAD, valvular dysfunction, or pericardial abnormalities. In 2006, the AHA classified cardiomyopathies as primary (genetic, mixed, or acquired) or secondary (infiltrative, toxic, inflammatory). The four major types of cardiomyopathy are dilated, hypertrophic, restrictive, and arrhythmogenic right ventricular.

Diagnosis

H&P
- Syncope
- VT
- Atypical chest pain
- Heart failure
- Sudden death

Labs
- BNP level, lytes, BUN, Cr, CPK

Imaging
- Echo: segmental wall abnormalities, w/ or w/o wall motion abnormalities
- ECG: Small-amplitude potentials at end of QRS complex (epsilon wave), abnl repolarization

Etiology
- Autosomal dominant

Treatment
- β-Blockers (sotalol)
- Antiarrhythmics (amiodarone)
- Catheter ablation
- Implantable cardioverter-defibrillator
- Cardiac transplantation

Clinical Pearl
- Cutaneous manifestations, such as extreme curly and kinked hair and palmomental keratoderma (Naxos disease), may be associated w/arrhythmogenic right ventricular cardiomyopathy.

92 CARDIOMYOPATHY, DILATED (CONGESTIVE)

Definition
Disease primarily involving the myocardium and characterized by myocardial dysfunction that is not the result of HTN, CAD, valvular dysfunction, or pericardial abnormalities. In dilated cardiomyopathy, the heart is enlarged and both ventricles are dilated.

Diagnosis

H&P
- Pulmonary rales, hepatomegaly, peripheral edema
- ↑ JVP
- ↓ Pulse pressure
- S₃, S₄
- MR, TR (less common)

Labs
- BNP, lytes, BUN, Cr, CK

Imaging
- CXR: cardiac enlargement, possible interstitial pulmonary edema
- Echo: ↓ EF w/global akinesia
- ECG: LVH w/ST-T wave changes, RBBB or LBBB, arrhythmias (AF, PVC, PAC, VT)
Etiology
- Idiopathic
- Alcoholism (15%-40% of all cases in Western countries)
- Collagen-vascular disease (SLE, RA, polyarteritis, dermatomyositis)
- Post myocarditis
- Peripartum (last trimester of pregnancy or 6 mo post partum)
- Heredofamilial neuromuscular disease
- Toxins (cobalt, lead, phosphorus, CO, mercury, doxorubicin, daunorubicin)
- Nutritional (beriberi, selenium deficiency, carnitine deficiency, thiamine deficiency)
- Cocaine, heroin, organic solvents ("glue sniffer’s heart")
- Irradiation
- Acromegaly, osteogenesis imperfecta, myxedema, thyrotoxicosis, diabetes
- Hypocalcemia
- Antiretroviral agents (zidovudine, didanosine, zalcitabine)
- Phenothiazines
- Infections (viral [HIV], rickettsial, mycobacterial, toxoplasmosis, trichinosis, Chagas’ disease)
- Hematologic (e.g., sickle cell anemia)

Treatment
- Treat CHF (cause of death in 70% of pts) w/sodium restriction, diuretics, ACEIs, β-blockers, spironolactone, and digitalis.
- Vasodilators (combined w/nitrates and ACEIs) are effective agents in all symptomatic pts w/left ventricular dysfunction.
- Prevent thromboembolism w/oral anticoagulants in all pts w/AF and in pts w/moderate or severe failure.
- Low-dose β-blockade w/carvedilol or other β-blockers may improve ventricular function by interrupting the cycle of reflex sympathetic activity and controlling tachycardia.
- Diltiazem and ACEIs have also been reported to have a long-term beneficial effect in idiopathic dilated cardiomyopathy.
- Use antiarrhythmic treatment as appropriate. Empiric pharmacologic suppression of asymptomatic ventricular ectopy does not ↓ risk of sudden death or improve long-term survival. In pts w/severe left ventricular dysfunction or symptomatic and sustained VT, the use of an automatic implantable cardioverter-defibrillator should be considered.
- Pts w/dilated cardiomyopathy (LVEF <25%) and associated coronary atherosclerosis (angina, ECG changes, reversible defects on thallium scan) may benefit from surgical revascularization.
- Consider heart transplantation for young pts (<60 yr old) who are no longer responsive to medical Rx. Dilated cardiomyopathy is the reason for 45% of heart transplantsations.

Clinical Pearl
- Vulnerability to cardiomyopathy among chronic alcohol abusers is partially genetic and is related to the presence of ACE DD genotype.

CARDIOMYOPATHY, HYPERTROPHIC OBSTRUCTIVE (HOCM, HCM, IHSS)

Definition
Disease primarily involving the myocardium and characterized by myocardial dysfunction that is not the result of HTN, CAD, valvular dysfunction, or pericardial abnormalities. In HOCM, there is marked hypertrophy of the myocardium and disproportionally greater thickening of the intraventricular septum than that of the free wall of the LV (asymmetric septal hypertrophy).

Diagnosis
H&P
- Dyspnea
- Syncope (usually seen w/exercise)
- Angina (↓ angina in recumbent position)
- Palpitations
- PE: harsh, systolic, diamond-shaped murmur at the LSB or apex that ↑ w/Valsalva maneuver and ↓ w/squatting
Diseases

Restrictive cardiomyopathy

Chapter 3 Diseases and Disorders

Imaging
- Two-dimensional echo: ventricular hypertrophy, ratio of septum thickness to left ventricular wall thickness >1.3:1, ↑ EF
- MRI useful in identifying segmental LVH undetectable by echocardiography
- CXR: nl or cardiomegaly
- ECG (abnl in 75%-95% pts): LVH, abnl Q waves in anterolateral and inferior leads
- 24-hr Holter monitor to screen for potential lethal arrhythmias (principal cause of syncope or sudden death in obstructive cardiomyopathy)

Etiology
- Autosomal dominant trait w/variable penetrance caused by mutations in any of 1-10 genes, each encoding proteins of cardiac sarcomere
- Sporadic occurrence

Treatment
- β-Blockers (e.g., propranolol 160-240 mg/day); ↓ HR = prolongation of diastole, = ↑ passive ventricular filling
- Verapamil also ↓ left ventricular outflow obstruction by improving filling and probably reducing myocardial ischemia.
- IV saline infusion in addition to propranolol or verapamil is effective in pts w/CHF.
- Disopyramide is a useful antiarrhythmic because it is also a negative inotrope.
- Avoid use of digitalis, diuretics, nitrates, and vasodilators.
- DDD pacing for hemodynamic and symptomatic benefit in pts w/drug-resistant HOCM. Implantation of a dual-chamber pacemaker however has not been shown to result in significant improvement in objective measures of exercise capacity.
- ICD for pts prone w/prior cardiac arrest or sustained spontaneous VT.
- Surgical treatment (myotomy-myectomy) is reserved for pts who have both a large outflow gradient (≥50 mm Hg) and severe sx of heart failure that are unresponsive to medical Rx. The risk of sudden death from arrhythmias is not altered by surgery.

Clinical Pearls
- HOCM is not a static disease. Some adults may experience subtle regression in wall thickness; others (approximately 5%-10%) paradoxically evolve into an end stage resembling dilated cardiomyopathy and characterized by cavity enlargement, LV wall thinning, and diastolic dysfunction.
- Pts w/HOCM are at ↑ risk of sudden death, especially if there is onset of sx during childhood. Left ventricular outflow at rest is also a strong, independent predictor of severe sx of heart failure and of death.

CARDIOMYOPATHY, RESTRICTIVE

Definition
Disease primarily involving the myocardium and characterized by myocardial dysfunction that is not the result of HTN, CAD, valvular dysfunction, or pericardial abnormalities. Restrictive cardiomyopathies are characterized by ↓ ventricular compliance, usually secondary to infiltration of the myocardium.

Diagnosis
H&P
- PE: edema, ascites, hepatomegaly, distended neck veins, regurgitant murmur, prominent apical impulse, Kussmaul’s sign
- Fatigue and weakness (secondary to ↓ output)

Imaging
- Echo: ↑ wall thickness and thickened cardiac valves (especially in pts w/ amyloidosis)
- Cardiac cath can be used to distinguish restrictive cardiomyopathy from constrictive pericarditis. MRI may also be useful to distinguish restrictive cardiomyopathy from constrictive pericarditis (thickness of the pericardium >5 mm in the latter).
CXR: moderate cardiomegaly, CHF (pulmonary vascular congestion, pleural effusion)
ECG: ↓ voltage w/ST-T wave changes; arrhythmias, LAD, and AF may also be present.

**Etiology**
- Infiltrative and storage disorders (glycogen storage disease, amyloidosis, sarcoidosis, hemochromatosis)
- Scleroderma
- Radiation
- Endocardial fibroelastosis
- Endomyocardial fibrosis
- Idiopathic
- Anthracycline
- Carcinoid heart disease, metastatic cancers
- Diabetic cardiomyopathy
- Eosinophilic cardiomyopathy (Löffler’s endocarditis)

**Treatment**
- Hemochromatosis: repeated phlebotomies to ↓ iron deposition in the heart
- Sarcoidosis: corticosteroid therapy
- Corticosteroid and cytotoxic drugs may improve survival in pts w/ eosinophilic cardiomyopathy.
- There is no effective Rx for other causes of restrictive cardiomyopathy.

**Clinical Pearl**
- Death usually results from CHF or arrhythmias; therefore, Rx should be aimed at controlling CHF by restricting salt, administering diuretics, and treating potentially fatal arrhythmias.

### CAROTID SINUS SYNDROME

**Definition**
Lightheadedness, dizziness, presyncope, or syncope in a pt w/carotid sinus hypersensitivity. Carotid sinus hypersensitivity is the exaggerated response to carotid stimulation resulting in bradycardia, hypotension, or both.

**Diagnosis**

**H&P**
- Usually associated w/sudden neck movements or tight-fitting collars
- Prodrome of nausea, warmth, pallor, or diaphoresis
- Lightheadedness or presyncopal sx
- Syncope
- Carotid sinus massage (CSM) at the bedside is diagnostic:
  - Performed in the supine and upright positions while monitoring the pt’s BP by cuff and HR by ECG
  - Performed on only one artery at a time
  - Applied for approximately 5-10 sec and repeated on the opposite side if no effect is produced
  - Contraindications to CSM include the presence of carotid artery bruits, documented carotid artery stenosis >70%, h/o stroke or TIA <3 mo, h/o MI <6 mo, h/o serious cardiac arrhythmias, and prior carotid endarterectomy.

**Etiology**
- Idiopathic
- Head and neck tumors (e.g., thyroid)
- Significant lymphadenopathy
- Carotid body tumors
- Prior neck surgery

**Treatment**
- For symptomatic pts w/a cardioinhibitory response to CSM: dual-chamber permanent pacemaker
- For symptomatic pts w/a vasodepressor response to CSM:
  - Sympathomimetics: midodrine 2.5-10 mg tid
  - Serotonin reuptake inhibitors
CARPAL TUNNEL SYNDROME

Definition
Focal entrapment syndrome involving the median nerve as it passes in the area between the bones of the wrist and the transverse carpal ligament.

Diagnosis
H&P
- Numbness and pain in the distal arm or wrist. Exacerbated by movement, typically radiates on the palmar surface of the lateral three digits of the hand. Nocturnal pain is common. Pain may radiate cephalad to shoulder.
- Tinel’s sign: tapping over the median nerve on the flexor surface of the wrist produces a tingling sensation radiating from the wrist to the hand.
- Phalen’s test: flexing the wrist 90 degrees for 1 min causes numbness and dysesthesias in the distribution of the median nerve.

EMG
- Dx is confirmed w/nerve conduction studies (if necessary, and pt is considering surgery).

Etiology
- Repeated trauma, post injury, rheumatoid tenosynovitis, pregnancy, hypothyroidism, acromegaly, diabetes, mass lesions (lipoma, ganglion, neoplasm), aberrant anatomy, edema, amyloid, wristFx

Treatment
- Minimize wrist movement (wrist splint, improved positioning of computer keyboard)
- NSAIDs
- Corticosteroid wrist injections: result in improvements in 50%-80% of those affected, although the majority of those experience recurrence.
- Surgical carpal tunnel release if the preceding measures are ineffective. Surgical division of the transverse carpal ligament relieves sensory complaints in >90% of pts.

CAT-SCRATCH DISEASE (BARTONELLOSIS)

Diagnosis
H&P
- Regional lymphadenopathy occurring within 2 wk of a scratch or contact w/felines
- Tender, swollen lymph nodes most commonly found in the head and neck, followed by the axilla and the epitrochlear, inguinal, and femoral areas
- Erythematous overlying skin, showing signs of suppuration from involved lymph nodes
- Evidence of cutaneous inoculation in the form of a nonpruritic, slightly tender pustule or papule

Labs
- Histology of lymph node biopsy specimen consistent w/cat-scratch disease
- Enhanced culture techniques and serologies augment establishment of the dx. An IFA Bartonella serology is commercially available. A PCR is used in research settings.
- Histopathologically, Warthin-Starry silver stain has been used to identify the bacillus.
- Abnormalities of bili excretion and ↑ hepatic transaminases are usually secondary to hepatic obstruction by granuloma, mass, or lymph node.

Etiology
- Major cause: Bartonella (Rochalimaea) henselae
- Mode of transmission: predominantly by direct inoculation through the scratch, bite, or lick of a cat, especially a kitten
Treatment
- *Bartonella* is usually sensitive to a 5-day course of azithromycin; alternatively, AGs, tetracycline, and the quinolones can be used.
- When the isolate is proven by culture, the pt should receive abx Rx as directed by the obtained susceptibilities.
- Antipyretics and NSAIDs may also be used.

Clinical Pearl
- A presentation of this syndrome, especially in pts w/HIV infection or impaired cellular immunity, may be FUO.

98 Cavernous Sinus Thrombosis (CST)

Diagnosis

H&P
- Ptosis
- Proptosis
- Chemosis
- Cranial nerve palsies (III, IV, V, VI)
- Sixth nerve palsy is the most common.
- Sensory deficits of the ophthalmic and maxillary branch of the fifth nerve are common.

Labs
- CBC, ESR, blood cultures, and sinus cultures help establish and identify an infectious primary source.
- LP is necessary to r/o meningitis.

Imaging
- MRI w/gadolinium including MR angiography is more sensitive than CT scan and is the imaging study of choice to diagnose CST.

Etiology
- *S. aureus* is the most common infectious microbe, found in 50%-60% of cases.
- *Streptococcus* is the second leading cause.
- Gram-negative rods and anaerobes may also lead to CST.
- The most common primary site of infection leading to CST is sphenoid sinusitis; however, other sites of infection, including the middle ear, orbit, eye, eyelid, and face, can result in the same sequelae.

Treatment
- Rx should take into account the primary source of infection as well as possible associated complications, such as brain abscess, meningitis, or subdural empyema.
- Broad-spectrum IV abx are used as empiric Rx until a definite pathogen is found. Treatment should include a penicillinase-resistant PCN at maximum dose plus a third- or fourth-generation ceph:
  - Nafcillin (or oxacillin) 2 g IV q4h plus either ceftriaxone (2 g q12h) or cefepime (2 g q6h).
  - Metronidazole 500 mg IV q6h should be added if anaerobic bacterial infection is suspected (dental or sinus infection).
- Vancomycin (1 g q12h w/nl renal function) may be substituted for nafcillin if significant concern exists for infection by MRSA or resistant *Streptococcus pneumoniae*.
- Anticoagulation w/heparin: controversial. Cerebral infarction or ICH should first be ruled out by non-contrast-enhanced CT scan before initiation of heparin Rx. Current recommendation is for early heparinization in pts w/unilateral CST to prevent clot propagation and to ↓ the incidence of septic emboli. Warfarin Rx should be avoided in the acute phase of the illness but should ultimately be instituted to achieve an INR of 2-3 and continued until the infection, sx, and signs of CST have resolved or significantly improved.
- Steroid Rx: controversial but may prove helpful in reducing cranial nerve dysfunction or when progression to pituitary insufficiency occurs. Corticosteroids should be instituted only after appropriate abx coverage. Dexamethasone 10 mg q6h is the treatment of choice.
Diseases

- Skin inflammatory condition characterized by erythema, warmth, and tenderness of the area involved.

99 CELIAC DISEASE

**Definition**
Chronic disease characterized by malabsorption and diarrhea precipitated by ingestion of food products containing gluten.

**Diagnosis**

**H&P**
- Weight loss, dyspepsia, short stature, and failure to thrive in children and infants
- Weight loss, fatigue, and diarrhea in adults
- Pallor as a result of iron deficiency anemia
- Atypical forms of the disease: osteoporosis, anemia, infertility, and neurologic problems
- Angular cheilitis, aphthous ulcers, atopic dermatitis, and dermatitis herpetiformis are frequently associated w/celiac disease
- PE: may be entirely within nl limits

**Labs**
- Iron deficiency anemia (microcytic anemia, ↓ ferritin level)
- Folic acid deficiency
- Vitamin B₁₂ deficiency, ↓ Mg, ↓ Ca
- IgA tissue transglutaminase (TTG) Ab by ELISA is an accurate serologic test for celiac sprue. Other useful tests are antiendomysial Ab and anti-gliadin antibodies.
- Bx of the small bowel is the gold standard for diagnosis of celiac disease. It is however invasive and not always necessary. It may be reasonable in children w/significant ↑ of TTG levels (>100 U) to first try a gluten-free diet and to consider bx only in those who do not improve w/diet.

**Etiology**
- Autoimmune-type disease w/TTG suggested as a major autoantigen. There is sensitivity to gliadin, a protein fraction of gluten found in wheat, rye, and barley.

**Treatment**
- Gluten-free diet (avoidance of wheat, rye, and barley). Safe grains (gluten free) include rice, corn, oats, buckwheat, millet, aranth, quinoa.
- Correct nutritional deficiencies w/iron, folic acid, Ca, vitamin B₁₂ as needed.
- Prednisone 20-60 mg qd gradually tapered is useful in refractory cases.

**Clinical Pearls**
- Celiac disease should be considered in pts w/unexplained metabolic bone disease or hypocalcemia, especially because GI sx may be absent or mild. Clinicians should also consider testing children and young adults for celiac disease if unexplained weight loss, abd pain or distention, and chronic diarrhea are present.
- Pts w/celiac disease have an overall risk of cancer that is almost 2× that in the general population: ↑ risk of adenocarcinoma of the small intestine and non-Hodgkin’s lymphoma, especially of T-cell type and primarily localized in the gut.

100 CELLULITIS

**Definition**
Superficial inflammatory condition of the skin characterized by erythema, warmth, and tenderness of the area involved.
Diagnosis

H&P

Physical presentation varies w/the causative organism:
- Erysipelas: superficial spreading, warm, erythematous lesion distinguished by its indurated and elevated margin; lymphatic involvement and vesicle formation are common.
- Staphylococcal cellulitis: area involved is erythematous, hot, and swollen; differentiated from erysipelas by nonelevated, poorly demarcated margin; local tenderness and regional adenopathy are common; up to 85% of cases occur on the legs and feet.
- H. influenzae cellulitis: area involved is blue-red/purple-red; occurs mainly in children; generally involves the face in children and the neck or upper chest in adults.
- Vibrio vulnificus: larger hemorrhagic bullae, cellulitis, lymphadenitis, myositis; often found in critically ill pts in septic shock.

Labs
- Often not necessary. In severe cases: CBC w/diff, Gram stain and culture (aerobic and anaerobic), blood cultures, ASO titer (in suspected streptococcal disease).

Etiology
- Group A beta-hemolytic streptococci (may follow a streptococcal infection of the upper respiratory tract)
- Staphylococcal cellulitis
- H. influenzae
- Vibrio vulnificus: higher incidence in pts w/liver disease (75%) and in immunocompromised hosts (corticosteroid use, DM, leukemia, renal failure)
- Erysipelothrix rhusiopathiae: common in people handling poultry, fish, or meat
- Fungi (Cryptococcus neoformans): immunocompromised granulopoenic pts
- Gram-negative rods (Serratia, Enterobacter, Proteus, Pseudomonas): immunocompromised or granulopoenic pts

Treatment

Erysipelas
- PO: dicloxacillin 500 mg PO q6h
- IV: cefazolin 1 g q6-8h or nafcillin 1.0-1.5 g IV q4-6h

NOTE: Use erythromycin, clindamycin, or vancomycin in pts allergic to PCN.

Staphylococcus Cellulitis
- PO: dicloxacillin 250-500 mg qid
- IV: nafcillin 1-2 g q4-6h
- Cephs (cephalothin, cepalexin, cephradine) also provide adequate antistaphylococcal coverage except for MRSA.
- Use vancomycin 1.0-2.0 g IV qd or linezolid 0.6 g IV q12h in pts allergic to PCN or cephs and in pts w/MRSA. Daptomycin (Cubicin), 4 mg/kg IV given over 30 min q24h is also effective. Other agents that may be effective against some strains of MRSA include quinupristin-dalfopristin (Synercid) and TMP-SMZ.

H. influenzae Cellulitis
- PO: cefixime or cefuroxime
- IV: cefuroxime or ceftriaxone

Vibrio vulnificus
- Doxycycline 100 mg IV bid + ceftazidime 2 g IV q8h or IV ciprofloxacin 400 mg bid. Mild cases can be treated w/oral abx (doxycycline 100 mg bid + ciprofloxacin 750 mg bid).
- IV support and admission into ICU (mortality rate >50% in septic shock)

Erysipelothrix
- PCN

Aeromonas hydrophila
- AGs
- Chloramphenicol
Complicated skin and skin structure infections in hospitalized pts can be treated w/daptomycin (Cubicin) 4 mg/kg IV q24h.

Clinical Pearls
- Cellulitis occurs most frequently in diabetics, immunocompromised hosts, and pts w/venous and lymphatic compromise.
- Frequently found near skin breaks (trauma, surgical wounds, ulcerations, tinea infections)

101 CHANCROID
Definition
STD characterized by painful genital ulceration and inflammatory inguinal adenopathy.

Diagnosis
- 1-3 extremely painful ulcers accompanied by tender inguinal lymphadenopathy (especially if fluctuant)
- May present w/inguinal bubo and several ulcers
- In women: initial lesion in the fourchette, labia minora, urethra, cervix, or anus; inflammatory pustule or papule that ruptures, leaving a shallow, nonindurated shallow ulceration, usually 1-2 cm diameter w/ragged, undermined edges
- Unilateral lymphadenopathy develops 1 wk later in 50% of pts.
- Definitive dx is made by isolation of organism from ulcers by culture or Gram stain. Darkfield microscopy, rapid plasma reagin, HSV cultures, H. ducreyi culture, and HIV testing are recommended.

Etiology
- Haemophilus ducreyi, a bacillus

Treatment
- Azithromycin 1 g PO (single dose) or
- Ceftriaxone 250 mg IM (single dose) or
- Ciprofloxacin 500 mg PO bid for 3 days (contraindicated in pts who are pregnant, lactating, or <18 yr old) or
- Erythromycin 500 mg PO qid for 7 days
- HIV-infected pts may need more prolonged Rx.

Clinical Pearls
- All sexual partners should be treated w/one of the previous regimens.
- Pts should be re-examined 3-7 days after initiation of Rx. Ulcers should improve symptomatically within 3 days and objectively within 7 days after initiation of successful Rx.

102 CHLAMYDIA GENITAL INFECTIONS
Definition
Genital infection w/Chlamydia trachomatis may result in urethritis, epididymitis, cervicitis, and acute salpingitis, but often it is asymptomatic in women. In men, sx include urethritis, mucopurulent d/c, dysuria, urethral pruritus.

Diagnosis
H&P
- Clinical manifestations may be similar to those of gonorrhea: mucopurulent endocervical d/c w/edema, erythema, and easily induced endocervical ulceration caused by inflammation of endocervical columnar epithelium. Less frequent manifestations may include Bartholinitis, urethral syndrome w/dysuria and pyuria, perihepatitis (Fitz-Hugh–Curtis syndrome).

Labs
- Cell culture is the reference method for dx (single culture sensitivity 80%-90%), but it is labor-intensive and takes 48-96 hr; it is not suited for large screening programs.
- Nonculture methods:
  - DFA
  - EIA
  - DNA probes
  - PCR
• W/the exception of PCR, the other tests are probably less specific than cell culture and may yield false + results.
■ Because this is an intracellular organism, purulent d/c is not an appropriate specimen. An adequate sample of infected cells must be obtained.

**Etiology**
■ *Chlamydia trachomatis*, serotypes D through K

**Treatment**

**NGU, urethritis, cervicitis, conjunctivitis (except for lymphogranuloma venereum):**
■ Azithromycin 1 g PO × 1 or
■ Doxycycline 100 mg PO bid for 7 days
■ Alternatives
  ■ Erythromycin base 500 mg PO qid for 7 days *or*
  ■ Erythromycin ethylsuccinate 800 mg PO qid for 7 days *or*

**Infection in pregnancy:**
■ Erythromycin base 500 mg PO qid for 7 days *or*
■ Amoxicillin 500 mg PO tid for 7 days
■ Alternatives:
  ■ Erythromycin base 250 mg PO qid for 7 days *or*
  ■ Erythromycin ethylsuccinate 800 mg PO qid for 7 days *or*
  ■ Erythromycin ethylsuccinate 400 mg PO qid for 14 days *or*
  ■ Azithromycin 1 g PO (single dose)

**Clinical Pearls**
■ *Chlamydia trachomatis* is the most common cause of STD in the U.S.
■ When treating chlamydia, it is best to assume concomitant gonorrhea since co-infection is common. Combination of PO ceftriaxone 125 mg IM single dose plus azithromycin 1 g PO single dose will treat both.

### 103 CHOLANGITIS

**Definition**
Inflammation or infection of the hepatic and CBDs associated w/obstruction of the CBD.

**Diagnosis**

**H&P**
■ Charcot’s triad: fever, RUQ pain, jaundice
■ Often, dark coloration of the urine resulting from bilirubinuria

**Labs**
■ ↑ WBC, ↑ alk phos and bili in chronic obstruction, ↑ transaminases in acute obstruction. *+ Blood cultures in 50% of cases, typically w/enteric gram-negative aerobes (e.g., *E. coli*, *Klebsiella pneumoniae*), enterococci, or anaerobes*

**Imaging**
■ U/S: insensitive but specific for visualization of common duct stones
■ CT scan: less accurate for gallstones but more sensitive than U/S for visualization of the distal part of the CBD
■ ERCP: if U/S and CT scan are inconclusive; confirms obstruction and its level and allows collection of specimens for culture and cytology

**Etiology**
■ Obstruction of the CBD causing rapid proliferation of bacteria in the biliary tree
■ Most common cause of CBD obstruction: stones, usually migrated from the gallbladder
■ Other causes: prior biliary tract surgery w/secondary stenosis, tumor (usually arising from the pancreas or biliary tree), and parasitic infections from *Ascaris lumbricoides* or *Fasciola hepatica*
■ Iatrogenic after contamination of an obstructed biliary tree by ERCP or percutaneous transhepatic cholangiography
■ PSC
■ HIV-associated sclerosing cholangitis: associated w/infection by CMV, *Cryptosporidium*, *Microsporidia*, and *Mycobacterium avium* complex
### Treatment
- Broad-spectrum abx directed at gram-neg enteric organisms, anaerobes, and enterococcus: if infection is nosocomial, post-ERCP, or the pt is in shock, broader coverage to include hospital organisms such as *Pseudomonas aeruginosa*, MRSA
- Biliary decompression in severely ill pts or those unresponsive to medical Rx within 12-24 hr. May also be performed semielectively in pts who respond. Options include ERCP w/ or w/o sphincterotomy or placement of a draining stent, percutaneous transhepatic biliary drainage for the acutely ill pt who is a poor surgical candidate, and surgical exploration of the CBD.

### 104 CHOLECYSTITIS

#### Definition
Acute or chronic inflammation of the gallbladder.

#### Diagnosis
**H&P**
- Pain and tenderness in the right hypochondrium or epigastrium; pain possibly radiating to the infrascapular region. Palpation of the RUQ elicits marked tenderness and stoppage of inspired breath (*Murphy’s sign*). Exam may also reveal guarding, fever (33%), jaundice (25%-50%), palpable gallbladder (20%).
- N/V (>70%), fever and chills (>25%), and ingestion of large, fatty meals before onset of pain in the epigastrium and RUQ

#### Labs
- Leukocytosis (12,000-20,000) >70% of pts, ↑ alk phos, ALT, AST, bili; bili elevation >4 mg/dL is unusual and suggests presence of choledocholithiasis.

#### Imaging
- U/S of gallbladder: presence of stones, dilated gallbladder w/thickened wall and surrounding edema, fluid stranding
- HIDA scan: sensitivity and specificity >90% for acute cholecystitis. Test is reliable only when bili is <5 mg/dL. + Test = absence of gallbladder filling within 60 min after the administration of tracer.
- CT of abd: in cases of suspected abscess, neoplasm, or pancreatitis

#### Etiology
- Gallstones (>95% of cases)
- Ischemic damage to the gallbladder, critically ill pt (acalculous cholecystitis)
- Infectious agents, especially in pts w/AIDS (CMV, *Cryptosporidium*)
- Strictures of the bile duct
- Neoplasms, primary or metastatic

#### Treatment
- Cholecystectomy
- Conservative management w/IV fluids and abx (ampicillin-sulbactam 3 g IV q6h or piperacillin-tazobactam 4.5 g IV q8h) may be justified in some high-risk pts to convert an emergency procedure into an elective one w/a lower mortality.
- ERCP w/sphincterotomy and stone extraction can be performed in conjunction w/laparoscopic cholecystectomy for pts w/choledocholithiasis; 7%-15% of pts w/cholelithiasis also have stones in the CBD.

#### Clinical Pearl
- Complication rate is approximately 1% (hemorrhage and bile leak) for laparoscopic cholecystectomy and <0.5% (infection) w/open cholecystectomy.

### 105 CHOLEDOCHOLITHIASIS

#### Diagnosis
**H&P**
- Biliary colic, jaundice, dark urine, light or clay-colored stool, fever, chills
**Labs**
- ↑ Bili, alk phos, ALT, AST

**Imaging**
- U/S will identify only 60%-70% of common duct stones.
- MRCP: sensitivity 95%, specificity 89% at detecting cholelithiasis
- EUS
- ERCP has advantage of providing therapeutic option at time of dx. Complications (5% of pts) include pancreatitis and cholangitis.

**Treatment**
- Endoscopic sphincterotomy w/stone extraction

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**106 CHOLELITHIASIS**

**Definition**
Presence of calculi in the gallbladder.

**Diagnosis**

**H&P**
- PE nl unless pts have biliary colic; 80% of gallstones are asymptomatic.
- Typical sx of obstruction of the cystic duct include intermittent, severe, cramping pain in RUQ.
- Pain occurs mostly at night and may radiate to the back or right shoulder. It can last from a few minutes to several hours.

**Labs**
- NL unless pt has biliary obstruction (↑ alk phos, bili)

**Imaging**
- U/S of the gallbladder: sensitivity, 95%; specificity, 90%; the presence of dilated gallbladder w/thickened wall is suggestive of acute cholecystitis.
- HIDA scan can confirm acute cholecystitis (>90% accuracy).
- CBD stones can be detected noninvasively by MRCP or invasively by ERCP and intraoperative cholangiography.

**Etiology**
- 75% of gallstones contain cholesterol: usually associated w/obesity, female sex, DM; mixed stones are most common (80%); pure cholesterol stones account for only 10% of stones.
- 25% of gallstones are pigment stones (bili, Ca, and variable organic material) associated w/hemolysis and cirrhosis.
- 50% of mixed-type stones are radiopaque.

**Treatment**
- Asymptomatic pts do not require therapeutic intervention.
- Lap cholecystectomy. 5%-26% of pts will require conversion to an open procedure; most common reason is inability to clearly identify the biliary anatomy.

**Clinical Pearl**
- Pts w/at least one gallstone <5 mm in diameter have a >4× ↑ risk of presenting w/acute biliary pancreatitis.

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**107 CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)**

**Definition**
Chronic demyelinating disease of the spinal nerve roots and peripheral nerves characterized by weakness and sensory deficits.

**Diagnosis**

**H&P**
- Onset is over a period of weeks, months, or years.
- Sx may be both sensory (paresthesias, neuropathic pain, and numbness of the hands and feet) and motor (weakness).
- Postural instability, gait abnormalities, and proximal muscle weakness may become prominent late in the disease.
- Sensory findings on PE: impaired vibration and joint position sense more common than impaired light touch, pinprick, and temperature sensation.
Muscle weakness: usually distal and symmetric

Reflexes are usually ↓.

**Electrophysiology**

Nerve conduction studies offer the best combination of sensitivity and specificity for the dx of CIDP.

**Labs**

- LP: ↑ CSF protein (especially helpful if >100 mg/dL), no pleocytosis (<10 white cells)
- Serum protein electrophoresis and immunofixation electrophoresis to identify M-protein
- Urine protein electrophoresis
- Hepatitis and HIV serology
- FBS
- Bone marrow bx if a monoclonal gammopathy is identified to exclude myeloma or other plasma cell dyscrasias

**Imaging**

- Long bone skeletal survey to identify osteosclerotic myeloma

**Etiology**

- CIDP occurs as a primary (idiopathic) form and may also occur in association w/many systemic disorders.
- The most common systemic disorder associated w/CIDP is a monoclonal gammopathy.
- An association w/DM has been recognized more recently.
- CIDP may occasionally occur in the context of HIV and hepatitis B or C infection.

**Treatment**

- The 3 primary treatment modalities for CIDP are high-dose oral corticosteroids, IVIG, and plasma exchange.
- IVIG is usually administered at a dose of 2 g/kg divided during 3-5 days. Initial improvement is observed in ½ of pts. If there has been incomplete improvement or no major improvement, it is advised to repeat the course of IVIG in 1-2 mo. If there continues to be further improvement of sx after repeated administration of IVIG, monthly infusions may be necessary to maintain a response.
- Plasma exchange is usually performed every other day for approximately 4-6 wk. Like IVIG, plasma exchanges may be repeated on a regular basis if therapeutic benefit has been established.
- Oral prednisone is usually initiated at a dose of ~1 mg/kg/day. High-dose prednisone dosing should be maintained until a clinical response is achieved, typically within 4-8 wk, after which the dose may be slowly tapered. The goal is to maintain a clinical response w/the lowest possible dose administered on an alternate-day regimen.

**Clinical Pearls**

- IVIG, plasma exchange, and prednisone are usually required on a chronic basis to maintain a clinical response. The frequency and dosing requirements must be determined on an individual basis.
- Steroid-sparing agents, such as azathioprine, mycophenolate mofetil, MTX, cyclosporine, and cyclophosphamide, may sometimes be necessary to ↓ the maintenance dose of steroids or the frequency w/which IVIG or plasma exchange is administered.

### 108 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

**Definition**

COPD is an inflammatory respiratory disease caused by exposure to tobacco smoke. It is characterized by the presence of airflow limitation that is not fully reversible. Traditionally, COPD was described as encompassing emphysema, characterized by loss of lung elasticity and destruction of lung parenchyma w/enlargement of air spaces, and chronic bronchitis, characterized by obstruction of small airways and productive cough >3 mo in duration for >2 successive years. These terms are no longer included in the formal definition of COPD, although they are still used clinically.
Pts w/COPD have also been classically subdivided in two major groups on the basis of their appearance:

- **Blue bloaters** are pts w/chronic bronchitis; the name is derived from the bluish tinge of the skin (secondary to chronic hypoxemia and hypercapnia) and from the frequent presence of peripheral edema (secondary to cor pulmonale); chronic cough w/production of large amounts of sputum is characteristic.
- **Pink puffers** are pts w/emphysema; they have a cachectic appearance but pink skin (adequate oxygen saturation); SOB is manifested by pursed-lip breathing and use of accessory muscles of respiration.

**Diagnosis**

**H&P**

- Peripheral cyanosis, productive cough, tachypnea, tachycardia
- Dyspnea, pursed-lip breathing w/use of accessory muscles for respiration, ↓ breath sounds, wheezing
- Acute exacerbation of COPD is mainly a clinical dx and generally is manifested w/worsening dyspnea, ↑ sputum purulence and volume.

**Labs**

- CBC may reveal leukocytosis w/shift to the left during acute exacerbation.
- Sputum may be purulent w/bacterial respiratory tract infections. Sputum staining and cultures are usually reserved for cases that are refractory to abx Rx.
- ABGs: normocapnia, mild to moderate hypoxemia may be present.
- Spirometry: the primary physiologic abnormality in COPD is ↓ in FEV₁. PFTs can be used to estimate disease severity in COPD as follows:
  - Mild COPD: FEV₁/FVC <0.70; FEV₁ ≥80% of predicted
  - Moderate COPD: FEV₁/FVC <0.70; FEV₁ 50%-79% of predicted
  - Severe COPD: FEV₁/FVC <0.70; FEV₁ 30%-49% of predicted
  - Very severe COPD: FEV₁/FVC <0.70; FEV₁ <30% of predicted or <50% of predicted w/chronic respiratory failure (SaO₂ <88%)
- Pts w/COPD can generally be distinguished from asthmatics by their incomplete response to albuterol (change in FEV₁ <200 mL and 12%) and absence of an abnl bronchoconstrictor response to methacholine or other stimuli (Table 3-8).

**TABLE 3-8 Pulmonary Function Test Patterns in Common Lung Diseases**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>FVC</th>
<th>FEV₁</th>
<th>FEV₁/FVC</th>
<th>RV</th>
<th>TLC</th>
<th>Diffusion (DLCo)</th>
<th>Bronchodilator Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>NI, ↑</td>
<td>NI, ↑</td>
<td>NI</td>
<td>+</td>
</tr>
<tr>
<td>Chronic obstructive bronchitis</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>NI, ↑</td>
<td>NI, ↑</td>
<td>NI</td>
<td>-</td>
</tr>
<tr>
<td>Chronic obstructive bronchitis w/ bronchospasm</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>NI, ↑</td>
<td>NI, ↑</td>
<td>NI</td>
<td>+</td>
</tr>
<tr>
<td>Emphysema</td>
<td>↓</td>
<td>NI, ↓</td>
<td>NI, ↑</td>
<td>NI, ↑</td>
<td>NI</td>
<td>NI, ↓</td>
<td>-</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>↓</td>
<td>NI, ↓</td>
<td>NI, ↑</td>
<td>NI, ↓</td>
<td>↓</td>
<td>↓</td>
<td>-</td>
</tr>
<tr>
<td>Obesity, kyphosis</td>
<td>↓</td>
<td>NI, ↓</td>
<td>NI, ↑</td>
<td>NI, ↓</td>
<td>↓</td>
<td>NI</td>
<td>-</td>
</tr>
</tbody>
</table>

↑, greater than predicted; ↓, less than predicted.

**Imaging**

**CXR:**

- Hyperinflation w/flattened diaphragm, tenting of the diaphragm at the rib, and ↑ retrosternal chest space, ↑ AP diameter
- ↓ Vascular markings and bullae in pts w/“emphysema”
Chapter 3 Diseases and Disorders

Thickened bronchial markings and enlarged right side of the heart in pts w/"chronic bronchitis"

Etiology
- Tobacco exposure
- Occupational exposure to pulmonary toxins (e.g., dust, noxious gases, vapors, fumes, cadmium, coal, silica). The industries w/the highest exposure risk are plastics, leather, rubber, and textiles.
- Atmospheric pollution
- AAT deficiency (<1% of COPD pts)

Treatment
- Avoidance of tobacco use and elimination of air pollutants
- Supplemental O₂, usually through nasal O₂ or a face mask to ensure oxygen saturation >90% measured by pulse oximetry. Indications for home O₂ Rx are PaO₂ < 55 mmHg or O₂ sat < 88%.
- Pulmonary toilet: careful nasotracheal suction is indicated only in pts w/excessive secretions and inability to expectorate.
- Pharmacologic treatment should be administered in a stepwise approach according to the severity of disease and pt’s tolerance for specific drugs.
  - Bronchodilators improve sx, quality of life, and exercise tolerance and ↓ incidence of exacerbations.
  - Anticholinergics (e.g., ipratropium inhaler 2 puffs qid) are effective first-line agents. They are available in combination w/albuterol (Combivent). Tiotropium (Spiriva HandiHaler) is a long-acting bronchodilator. It is effective for the long-term, once-a-day maintenance treatment of bronchospasm.
  - Short-acting β₂ agonists (e.g., albuterol MDI 1-2 puffs q4-6h PRN) are acceptable in pts w/mild, variable sx. Long-acting inhaled agents (e.g., salmeterol or formoterol 1-2 puffs bid) are useful in pts w/mild to moderate or continuous sx.
  - Addition of inhaled steroids (fluticasone, budesonide, triamcinolone) is used to ↓ exacerbations in pts w/moderate to severe COPD.
- Acute exacerbation of COPD can be treated with
  - Aerosolized β₂ agonists (e.g., metaproterenol nebulizer solution 5% 0.3 mL or albuterol nebulized 5% solution 2.5-5 mg)
  - Anticholinergic agents, which have equivalent efficacy to inhaled β-adrenergic agonists. Inhalant solution of ipratropium bromide 0.5 mg can be administered q4-8h and in combination with β₂ agonists.
  - Short courses of systemic corticosteroids have been shown to improve spirometric and clinical outcomes. In the hospital setting: IV methylprednisolone 50- to 100-mg bolus, then 40 mg q6-8h; taper as soon as possible. In the outpatient setting: PO prednisone 40 mg/day initially; ↓ the dose by 10 mg every other day.
  - NIPPV ↓ the risk of endotracheal intubation and ↓ ICU admission rates. Contraindications to its use are uncooperative pt, ↓ level of consciousness, hemodynamic instability, inadequate mask fit, and severe respiratory acidosis. ↑ Airway pressure can be delivered by inspiratory positive airway pressure, CPAP, or BiPAP, which combines the other modalities. When NIPPV is used, the nasal mask is usually tolerated the best.
  - The role of inhaled corticosteroids in COPD is controversial. Although some trials have demonstrated mild improvement in pts’ sx and ↓ frequency of exacerbations, most pulmonologists believe that these drugs are ineffective in most pts w/COPD but should be considered for pts w/moderate to severe airflow limitation who have persistent sx despite optimal bronchodilator Rx.
- Abx in suspected respiratory infection (e.g., ↑ purulence and volume of phlegm)
  - H. influenzae, S. pneumoniae are frequent causes of acute bronchitis.
  - PO abx of choice: azithromycin, levofloxacin, amoxicillin-clavulanate, and cefuroxime.
  - The use of abx is beneficial in exacerbations of COPD presenting w/↑ dyspnea and sputum purulence (especially if the pt is febrile).
Diseases may improve cough sx and mucus clearance; however, mucolytic medications are generally ineffective. Their benefits may be greatest in pts w/more advanced disease.

In pts w/end-stage emphysema who have an FEV₁ <25% of predicted nl value after administration of bronchodilator and additional complications such as severe hypoxemia, hypercapnia, and pulmonary HTN, single-lung transplantation should be considered a surgical option.

**CHURG-STRAUSS SYNDROME (ALLERGIC ANGIITIS, ALLERGIC GRANULOMATOSIS)**

**Definition**
Systemic vasculitis accompanied by severe asthma (core clinical feature), hypereosinophilia, and necrotizing vasculitis w/extravascular eosinophil granulomas.

**Diagnosis**

**H&P**
The clinical picture typically consists of 3 partially overlapping phases:

- The prodromal phase or allergic phase occurs in the second and third decades of life. It is characterized by severe adult-onset asthma, w/o allergic rhinitis, sinusitis, headache, cough, and wheezing. This phase precedes full development of the syndrome usually by several years.
- The eosinophilic phase is characterized by peripheral eosinophilia and eosinophil infiltration of the lungs, myocardium, and GI tract, w/o w/o granulomas, producing signs and sx of cough, fever, anorexia, weight loss, sweats, malaise, N/V, abd pain, and diarrhea.
- The systemic vasculitic phase, which appears approximately 3-8 yr after asthma, is characterized by the development of necrotizing vasculitis clinically apparent primarily in peripheral nerves, skin, and kidneys.

**Labs**
- CBC w/diff: eosinophilia
- ↑ ESR
- BUN/Cr may be ↑, suggesting renal involvement.
- U/A may show hematuria and proteinuria.
- 24-hr urine for protein >1 g/day is a poor prognostic factor.
- + ANCA in up to 70% of pts, usually w/a perinuclear staining pattern.
- Stools may be OB+ (enteric involvement during eosinophilic phase).
- ↑ AST, ALT, and CPK may indicate liver or muscle (skeletal or cardiac) involvement.
- RF and ANA may be +.
- Bx confirms the dx. Surgical lung bx is the gold standard. Necrotizing vasculitis and extravascular necrotizing granulomas, usually w/eosinophilic infiltrates, are suggestive of Churg-Strauss syndrome. The presence of eosinophils in extravascular tissues is most specific.

**Imaging**
- CXR abnl in 37%-77%: asymmetric patchy migratory infiltrates, ILD, or nodular infiltrates. Small pleural effusions are found in 29% of cases.
- Lung lesions in Churg-Strauss are noncavitating, as opposed to Wegener’s granulomatosis.
- Paranasal sinus films may reveal sinus opacification.
- Angiography is sometimes done in pts w/mesenteric ischemia or renal involvement.

**Etiology**
- Autoimmune disorder

**Treatment**
- Prednisone 1 mg/kg/day is the starting dose and is continued for 6-12 wk or until the disease has resolved. After clinically evident vasculitis resolves, prednisone is tapered progressively to 10 mg/day at 1 yr.
- Oxygen Rx in severe asthmatic exacerbations

**Clinical Pearls**
- Churg-Strauss is distinguished from other vasculitides by the nearly universal presence of asthma that typically precedes all other sx.
The asthma associated with Churg-Strauss is distinct from common allergic asthma in that it typically has a late onset and a degree of eosinophilia that is much greater than typically seen in allergic asthma. Patients typically have no FHx of allergies or asthma.

110 CIRRHOsis

Definition
Cirrhosis is defined histologically as the presence of fibrosis and regenerative nodules in the liver.

Diagnosis

H&P
- Jaundice; spider angiomas; ecchymosis; gynecomastia in men; small, nodular liver; ascites; hemorrhoids; testicular atrophy

Labs
- Alcoholic hepatitis and cirrhosis: mild ↑ ALT, AST, usually <500 IU; AST > ALT (ratio >2:3)
- Extrahepatic obstruction: moderate ↑ ALT and AST to levels <500 IU
- Viral, toxic, or ischemic hepatitis: ↑↑ (>500 IU) ALT, AST
- ↑ Alk phos elevation: extrahepatic obstruction, PBC, and PSC
- ↑ Serum LDH: metastatic disease of the liver, hepatitis, cirrhosis, extrahepatic obstruction, congestive hepatomegaly
- ↑ Serum GGTP: alcoholic liver disease, PBC, PSC
- ↑ Serum bili, + urinary bili: hepatitis, hepatocellular jaundice, biliary obstruction
- ↓ Serum alb: significant liver disease
- ↑ PT: severe liver damage and poor prognosis
- + HBsAg: acute or chronic hepatitis B
- + Antimitochondrial Abs: PBC, chronic hepatitis
- ↑ Serum copper, ↓ serum ceruloplasmin, and ↑ 24-hr: Wilson's disease
- ↓ α1-Globulins (α1-antitrypsin deficiency), ↑ IgA (alcoholic cirrhosis), ↑ IgM (PBC), ↑ IgG (chronic hepatitis, cryptogenic cirrhosis)
- ↑ Serum ferritin, ↑ transferrin saturation: hemochromatosis
- ↑ Blood ammonia: hepatocellular dysfunction
- + ANA: autoimmune hepatitis

Imaging
- U/S: for detection of gallstones and dilation of CBDs
- CT abd: for detection of mass lesions in liver and pancreas; assessment of hepatic fat content; identification of idiopathic hemochromatosis; early diagnosis of Budd-Chiari syndrome, dilation of intrahepatic bile ducts; and detection of varices and splenomegaly
- Percutaneous liver bx: evaluation of hepatic filling defects; diagnosis of hepatocellular disease or hepatomegaly; evaluation of persistently abnormal LFTs; and diagnosis of hemochromatosis, PBC, Wilson's disease, glycogen storage diseases, chronic hepatitis, autoimmune hepatitis, infiltrative diseases, alcoholic liver disease, drug-induced liver disease, and primary or secondary carcinoma

Etiology
- Alcohol abuse
- Secondary biliary cirrhosis, obstruction of the CBD (stone, stricture, pancreatitis, neoplasm, sclerosing cholangitis)
- Drugs (e.g., acetaminophen, isoniazid, MTX, methylprednisolone)
- Hepatic congestion (e.g., CHF, constrictive pericarditis, tricuspid insufficiency, thrombosis of the hepatic vein, obstruction of the vena cava)
- PBC
- Hemochromatosis
- Chronic hepatitis B or C
- Wilson's disease
- AAT deficiency
- Infiltrative diseases (amyloidosis, glycogen storage diseases, hemochromatosis)
- Nutritional: jejunooileal bypass
Others: parasitic infections (schistosomiasis), idiopathic portal HTN, congenital hepatic fibrosis, systemic mastocytosis, autoimmune hepatitis, hepatic steatosis, IBD

**Treatment**

- Variable w/etiology
- Liver transplantation: indicated in otherwise healthy pts (age <65 yr) w/sclerosing cholangitis, chronic hepatitis, cirrhosis, or PBC, w/prognostic information suggesting <20% chance of survival w/o transplantation. Contraindications to liver transplantation are AIDS, most metastatic malignant neoplasms, active substance abuse, uncontrolled sepsis, and uncontrolled cardiac or pulmonary disease.
- Treatment of complications of portal HTN (ascites, esophagogastric varices, hepatic encephalopathy, and HRS)

### CIRRHOSIS, PRIMARY BILIARY

**Definition**

Chronic disease characterized by progressive destruction of the small intrahepatic bile ducts w/portal inflammation leading to fibrosis, cirrhosis, and liver failure. Dx is based on 3 criteria (2 criteria indicate a probable dx, and all 3 criteria are required for a definite dx):

- + Antimitochondrial Abs, titer >1:40
- ↑ LFTs (especially alk phos) for >6 mo
- Characteristic liver histology: asymmetric destruction of the bile ducts within the portal triads

**Diagnosis**

**H&P**

- Clinical presentation: variable, depending on stage of dx: Typical patient is middle-aged female.
- Fatigue and pruritus are the usual presenting sx. 48%-60% may be asymptomatic.
- Musculoskeletal complaints caused by inflammatory arthropathy (40%-70% of pts), osteoporosis (20%-30%)
- Hepatomegaly, splenomegaly: present in more advanced disease

**Labs**

- + Antimitochondrial Abs (95% of pts, 98% specific), ↑↑ alk phos (of hepatic origin), ↑ GGTP, N↑ ALT, ↑ bili w/disease progression (direct and indirect), ↑ serum lipids (total cholesterol, LDL, and especially HDL), ↑ ceruloplasmin, eosinophilia, ↑ IgM
- Percutaneous liver bx: confirmatory test

**Treatment**

- Asymptomatic stage: follow bili every 3-4 mo; if it begins to rise, start ursodeoxycholic acid (UDCA).
- Rx focuses on management of complications (pruritus, metabolic bone diseases, hyperlipidemia) because liver transplantation is the only definitive treatment for this disease.
- 20% of pts will not respond to medical Rx and proceed to liver transplantation.
- Goals of treatment: resolution of pruritus, ↓ alk phos levels to <50% above nl, and improvement in liver bx histology.
- Ursodiol (12-15 mg/kg/day, divided or as one hs dose) significantly ↓ ascites, jaundice, and levels of bili and liver transaminases. Data are mixed as to whether ursodiol ↓ mortality, need for liver transplantation, pruritus, fatigue, quality of life, liver histology, or portal BPs.
- Colchicine (0.6 mg bid) and MTX (15 mg/wk) yield less impressive results but may be helpful.
- For the pruritus of PBC, cholestyramine resin (8-24 g qd) ↓ pruritus in most pts. UV light is also useful. Antihistamines at hs help nighttime sx. Rifampin (150 mg twice qd) is effective for those who do not respond to or tolerate resins. Naloxone and naltrexone are third-line agents, and plasmapheresis is helpful when all other therapies fail.
CLOSTRIDIAL MYONECROSIS (GAS GANGRENE)

Definition
Infection due to Clostridium perfringens and other Clostridium species.

Diagnosis
H&P
- Diffuse swelling and tenderness of affected area
- Systemic sx may include shock and organ failure
Labs
- Incision and probing of site, Gram stain, C&S
Imaging
- CT or MRI: useful in locating the site and depth of infection

Etiology
- Contaminated traumatic wound
- May also occur spontaneously w/o trauma

Treatment
- Surgical debridement in addition to abx. Prompt surgical treatment is necessary because of the rapidity of disease progression.
- Abx: PCN G 24 million units/day div q4-6h IV + clindamycin 900 mg IV q8h.
- Hyperbaric oxygen may be beneficial, especially if debridement is not complete or possible.

COCaine OVERDOSE

Diagnosis
H&P
- Phase I
  - CNS: euphoria, agitation, headache, vertigo, twitching, bruxism, nonintentional tremor
  - N/V, fever, HTN, tachycardia
- Phase II
  - CNS: lethargy, hyperreactive DTRs, seizures (status epilepticus)
  - Sympathetic overdrive: tachycardia, HTN, hyperthermia
  - Incontinence
- Phase III
  - CNS: flaccid paralysis, coma, fixed dilated pupils, loss of reflexes
  - Pulmonary edema
  - Cardiopulmonary arrest
- Psychological dependence is manifested w/habituation, paranoia, hallucinations (cocaine “bugs”).
- CNS: cerebral ischemia and infarction, cerebral arterial spasm, cerebral vasculitis, cerebral vascular thrombosis, subarachnoid hemorrhage, intraparenchymal hemorrhage, seizures, cerebral atrophy, movement disorders
- Cardiac: acute myocardial ischemia and infarction, arrhythmias and sudden death, dilated cardiomyopathy and myocarditis, infective endocarditis, aortic rupture
- Pulmonary (secondary to smoking crack cocaine)
  - Inhalation injuries: cartilage and nasal septal perforation, oropharyngeal ulcers
  - Immunologically mediated diseases: hypersensitivity pneumonitis, bronchiolitis obliterans; pulmonary vascular lesions and hemorrhage, pulmonary infarction, pulmonary edema secondary to left ventricular failure, pneumomediastinum, and pneumothorax
- GI: gastroduodenal ulceration and perforation; intestinal infarction or perforation, colitis
- Renal: ARF secondary to rhabd and myoglobinuria; renal infarction; focal segmental glomerulosclerosis
- Obstetric: placental abruption, low infant weight, prematurity, and microcephaly
- Psychiatric: anxiety, depression, paranoia, delirium, psychosis, and suicide
Diseases and Disorders

Labs
- Toxicology screen (urine): cocaine is metabolized within 2 hr by the liver to major metabolites, benzoylecgonine and ecgonine methylester, that are excreted in the urine. Metabolites can be identified in urine within 5 min of IV use and up to 48 hr after oral ingestion.
- Blood: CBC, lytes, glucose, BUN, Cr, Ca
- ABGs
- Serum CK and troponins

Imaging
- ECG

Treatment
- Inhalation: wash nasal passages.
- Agitation:
  - Check STAT glucose.
  - Diazepam 15-20 mg PO or 2-10 mg IM or IV for severe agitation
- Hyperthermia:
  - Check rectal temperature, CK, electrolytes.
  - Monitor w/continuous rectal probe; bring temperature down to 101°F within 30-45 min.
- Rhabdo:
  - Vigorous hydration w/urine output at least 2 mL/kg
  - Mannitol or bicarbonate for rhabdo resistant to hydration
- Seizure management (status epilepticus):
  - Diazepam 5-10 mg IV over 2-3 min; may be repeated every 10-15 min prn
  - Lorazepam 2-3 mg IV over 2-3 min can be used instead of diazepam
  - Phenytoin loading dose 15-18 mg/kg IV at a rate not to exceed 25-50 mg/min under cardiac monitoring
  - Phenobarbital loading dose 10-15 mg/kg IV at a rate of 25 mg/min; an additional 5 mg/kg may be given in 30-45 min if seizures are not controlled.
  - Refractory seizures, consider:
    - Pancuronium 0.1 mg/kg IV
    - Halothane general anesthesia
    - Both require EEG monitoring to determine brain seizure activity.
- HTN:
  - Cocaine-induced HTN usually responds to benzos. If this fails:
    - Consider A-line for continuous BP monitoring.
    - Avoid the use of CCBs (may potentiate the incidence of seizures and death, especially in body packers).
    - The use of β-blockers may exacerbate cocaine-induced vasoconstriction.
    - Phentolamine (unopposed adrenergic effects) or NTG may be required.
  - If diastolic pressure >120 mm Hg: hydralazine hydrochloride 25 mg IM or IV; may repeat q1h
  - If HTN uncontrolled or hypertensive encephalopathy is present: sodium nitroprusside initially at 0.5 µg/kg/min not to exceed 10 µg/kg/min
- Chest pain:
  - CXR, ECG, cardiac enzymes
  - Benzos for agitation
  - ASA and NTG for ischemic pain
  - Percutaneous transluminal coronary angioplasty may be preferred over thrombolysis for cocaine-associated MI
  - The use of β-adrenergic blockers remains controversial because of the unopposed α-adrenergic effects of cocaine.
  - The combination of nitroprusside and a β-adrenergic blocking agent or phentolamine alone or in addition to a β-adrenergic blocking agent may successfully treat myocardial ischemia and HTN.
- Ventricular arrhythmias:
  - Antiarrhythmia agents should be used w/caution during the early period after cocaine exposure as a result of their proarrhythmic and proconvulsant effects.
• Propranolol 1 mg/min IV for up to 6 mg (may result in unopposed α-adrenergic effects)
• Lidocaine 1.5 mg/kg IV bolus followed by IV infusion (controversial: may be proarrhythmic and proconvulsant)
• Termination of ventricular arrhythmias may be resistant to lidocaine and even cardioversion.
• NaHCO₃ Rx is under investigation in cocaine-mediated conduction abnormalities and rhythm disturbances.

Clinical Pearls
■ Cocaine-induced vasoconstriction may be exacerbated by the use of selective and nonselective β-adrenergic blocking agents.
■ The use of lidocaine in treating ventricular arrhythmias may precipitate seizures and further arrhythmias.

114 Coccidioidomycosis

Definition
Infectious disease caused by the fungus Coccidioides immitis. More common in southwestern U.S. (San Joaquin Valley fever)

Diagnosis

H&P
■ Asymptomatic infections or illnesses consistent w/a nonspecific URI in at least 60%. Spontaneous improvement within 2 wk of illness, w/complete recovery usual. Subsequent pulmonary residua in the form of pulmonary nodules and cavities in <10% of those pts w/primary infection.
■ Sx of primary infection—cough, malaise, fever, chills, night sweats, anorexia, weakness, and arthralgias (desert rheumatism)—in remaining 40% within 3 wk of exposure. Rashes, such as erythema nodosum and erythema multiforme, may occur. Some, especially if immunocompromised or diabetic, progress to chronic pulmonary disease. During many years, granulomas rupture, leading to new cavity formation and continued fibrosis, often accompanied by hemoptysis. Disseminated or extrapulmonary disease occurs in approximately 0.5% of acutely infected pts.

Labs
■ Definitive dx based on demonstration of the organism by culture from body fluids or tissues. Greatest yield w/pus, sputum, synovial fluid, and soft tissue aspirations, varying w/the degree of dissemination.
■ Serologic evaluations: latex agglutination and complement fixation;
  ↑ serum complement-fixing Ab (CFA) titers ≥1:32 strongly correlate w/disseminated disease, except w/meningitis, in which lower titers are seen.
■ Other labs: CBC may reveal eosinophilia, especially w/erythema nodosum;
  ↑ serum levels of IgE are associated w/progressive disease.

Imaging
■ CXR: unilateral infiltrates, hilar adenopathy, or pleural effusion in primary infection

Treatment
■ No drug Rx for pts w/asymptomatic pulmonary disease and most pts w/mild symptomatic primary infection
■ Extrapulmonary manifestations involving draining skin, joint, and soft tissue infection: local wound care to avoid possible bacterial superinfection
■ Chemotherapy: severe symptomatic primary infection, high serum CFA titers, persistent sx >6 wk, prostration, progressive pulmonary involvement, pregnancy, infancy, debilitation, concurrent illness (e.g., diabetes, asthma, COPD, malignant disease), acquired or induced immunosuppression
■ Fluconazol: 400 mg/day PO up to 1.2 g/day for meningeal and deep-seated mycotic infections
■ Itraconazol: 400-600 mg/day achieves 90% response rate in bone, joint, soft tissue, lymphatic, and GU infections.
■ For pulmonary infections, treatment w/either fluconazole or itraconazole, given for 6-12 wk, appears to be equal in efficacy.
Amphotericin B is the classic Rx for disseminated extraneural disease, dose 0.6-1.0 mg/kg/day, qd for the first wk and then 0.8 mg/kg every other day until clinical and serologic remission is accomplished.

Local instillation into body cavities such as sinuses, fistulas, and abscesses has been adjunct to Rx.

Liposomal amphotericin B 3-5 mg/kg/day is probably equally effective.

Duration of Rx for extraneural disease is undefined but probably about 1 yr.

With meningeal disease:
- Fluconazole 400-1000 mg PO q24h indefinitely.
- Intrathecal amphotericin B given alone or preceding the use of oral agents is an alternative treatment modality.
- Begin in doses of 0.01-0.025 mg/day, gradually increasing the dose as tolerated, to 0.5 mg/day w/the pt in Trendelenburg’s position.

COLORECTAL CANCER (CRC)

Definition
Neoplasm arising from the luminal surface of the large bowel: descending colon (40%-42%), rectosigmoid and rectum (30%-33%), cecum and ascending colon (25%-30%), transverse colon (10%-13%).

Classification and Staging
- Dukes’ and UICC classification for CRC:
  - A: Confined to the mucosa-submucosa (I)
  - B: Invasion of muscularis propria (II)
  - C: Local node involvement (III)
  - D: Distant mets (IV)

- TNM classification: Table 3-9.

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM Classification</th>
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<tr>
<td>IV</td>
<td>T (any), N (any), M1</td>
</tr>
</tbody>
</table>

Diagnosis

H&P
- The clinical presentation of colorectal malignant neoplasms is initially vague and nonspecific (weight loss, anorexia, malaise). It is useful to divide colon cancer sx into those usually associated w/right side of colon and those commonly associated w/left side of colon because the clinical presentation varies w/the location of the carcinoma.

- Right side of colon:
  - Anemia (iron deficiency secondary to chronic blood loss)
  - Dull, vague, and uncharacteristic abd pain may be present, or pt may be completely asymptomatic.
  - Rectal bleeding is often missed because blood is mixed w/feces (occult blood).
  - Obstruction and constipation are unusual because of large lumen and more liquid stools.
Diseases

COLORECTAL CANCER (CRC)

Chapter

Treatment

The backbone of treatment of CRC is fluorouracil. Leucovorin (folinic acid) enhances the effect of fluorouracil and is given together w/it.

Radiation Rx is a useful adjunct to fluorouracil and leucovorin Rx for stage II or III rectal cancers.

For pts w/standard-risk stage III tumors (e.g., involvement of 1-3 regional lymph nodes), both fluorouracil alone and fluorouracil w/oxaliplatin are reasonable choices. The oral fluoropyrimidine capecitabine is a prodrug that undergoes enzymatic conversion to fluorouracil. It is an effective alternative to IV fluorouracil as adjuvant treatment for stage III colon cancer because it has a lower incidence of mouth sores and bone marrow suppression. It does, however, have an ↑ incidence of palmar-plantar erythrodysesthesia (hand-foot syndrome).

Irinotecan can be used to treat metastatic CRC refractory to other drugs.

Oxaliplatin, a third-generation platinum derivative, can be used in combination w/fluorouracil and leucovorin for pts w/metastatic CRC whose disease has recurred or progressed despite treatment w/fluorouracil and leucovorin + irinotecan. Fluorouracil + oxaliplatin should be considered for high-risk pts w/stage III cancers (e.g., >3 involved regional nodes [N2] or tumor invasion beyond the serosa [T4 lesion]).

The monoclonal Abs cetuximab, panitumumab, and bevacizumab can be used for advanced CRC.

Clinical Pearl

The liver is generally the initial and most common site of CRC mets. Resection of mets limited to the liver is curative in more than 30% of selected pts. In pts who undergo resection of liver mets, postoperative treatment w/a combination of hepatic arterial infusion of floxuridine and IV fluorouracil improves the outcome at 2 yr.
**116 CONDYLOMA ACUMINATUM**

**Definition**
STD of the vulva, vagina, and cervix caused by HPV.

**Diagnosis**
- Lesions usually found in genital area but can be present elsewhere. There are four morphologic types: condylomatus, keratotic, papular, and flat warts.
- Initial lesions pedunculated, soft papules about 2-3 mm in diameter, 10-20 mm long; may occur as single papule or in clusters.
- Size of lesions varies from pinhead to large cauliflower-like masses. Usually asymptomatic, but if infected, can cause pain, odor, or bleeding.

**Treatment**

**Keratolytic Agents**
- Podophyllin: applied directly to lesion weekly and washed off in 6 hr
- Trichloroacetic acid (30%-80% solution): applied twice monthly to lesion; less painful and irritating to nl tissue than podophyllin
- Fluorouracil: causes necrosis and sloughing of growing tissue; can be used intravaginally or for vulvar, anal, or urethral lesions; applied weekly for 12 wk

**Physical Agents**
- Cryotherapy: can be used weekly for 3-6 wk, 62%-79% success rate; not suitable for large warts
- Laser Rx: painful, requires anesthesia
- Electrocautery or excision
- Immunotherapy
- Interferon: injected intralesionally at a dose of 3 million U/m^2^ 3x weekly for 8 wk
- Imiquimod 5% cream qd at hs 3x/week up to 16 weeks

**Clinical Pearls**
- Transmitted disease spread by skin-to-skin contact. Highly contagious, w/25%-65% of sexual partners developing it.
- Average incubation time is 2 mo (range: 1-8 mo).

**117 CONGESTIVE HEART FAILURE (CHF)**

**Definition**
Pathophysiologic state characterized by congestion in the pulmonary or systemic circulation. Due to the heart’s inability to pump sufficient oxygenated blood to meet the metabolic needs of the tissues. Systolic dysfunction refers to loss of contractile strength of myocardium in the setting of ventricular dilatation. Diastolic dysfunction occurs when filling of one or both ventricles is impaired in the setting of normal emptying capacity.

**Classification**
- The ACC and the AHA describe the following four stages of heart failure:
  - A: At high risk for heart failure, but w/o structural heart disease or sx of heart failure (e.g., CAD, HTN)
  - B: Structural heart disease but w/o sx of heart failure
  - C: Structural heart disease w/prior or current sx of heart failure
  - D: Refractory heart failure requiring specialized interventions
- The NYHA defines the following functional classes:
  - I: Asymptomatic
  - II: Symptomatic w/moderate exertion
  - III: Symptomatic w/min. exertion
  - IV: Symptomatic at rest

**Diagnosis**

**H&P**
- The findings on PE in pts w/CHF vary according to the severity and whether the failure is right sided or left sided.
- Common clinical manifestations are
  - Dyspnea on exertion initially, then w/progressively less strenuous activity, and eventually manifesting when pt is at rest; caused by ↑ pulmonary congestion
• Orthopnea caused by ↑ venous return in the recumbent position
• PND resulting from multiple factors (↑ venous return in the recumbent position, ↓ PaO₂, ↓ adrenergic stimulation of myocardial function)
• Nocturnal angina resulting from ↑ cardiac work (secondary to ↑ venous return)
• *Cheyne-Stokes respiration*: alternating phases of apnea and hyperventilation caused by prolonged circulation time from lungs to brain
• Fatigue, lethargy resulting from low CO
  - Left-sided heart failure: pulmonary rales, tachypnea, S₃ gallop, cardiac murmurs (AS, AR, MR), paradoxical splitting of S₂
  - Right-sided heart failure: JVD, peripheral edema, perioral and peripheral cyanosis, congestive hepatomegaly, ascites, HJR
• Acute precipitants of CHF exacerbations are noncompliance w/salt restriction, pulmonary infections, arrhythmias, medications (e.g., CCBs, antiarrhythmic agents), and inappropriate reductions in CHF Rx.

**Labs**
- CBC (to r/o anemia, infections), BUN, Cr, lytes, liver enzymes, TSH
- ↑ BNP

**Imaging**
- CXR: pulmonary venous congestion, cardiomegaly w/dilation of the involved heart chamber, pleural effusions
- 2D echo: useful to assess global and regional LV function and to estimate EF

**Etiology**

**Left Ventricular Failure**
- HTN
- Valvular heart disease (AS, AR, MR)
- Cardiomyopathy, myocarditis
- Bacterial endocarditis
- MI
- IHSS
- Left ventricular failure is further differentiated according to systolic dysfunction (↓ EF) and diastolic dysfunction (N/↑), or “stiff ventricle.”
- Common causes of systolic dysfunction are post-MI, cardiomyopathy, myocarditis.
- Causes of diastolic dysfunction are hypertensive CVD, valvular heart disease (AS, AR, MR, IHSS), restrictive cardiomyopathy.

**Right Ventricular Failure**
- Valvular heart disease (mitral stenosis)
- Pulmonary HTN
- Bacterial endocarditis (right sided)
- Right ventricular infarction

**Biventricular Failure**
- Left ventricular failure
- Cardiomyopathy
- Myocarditis
- Arrhythmias
- Anemia
- Thyrotoxicosis
- AV fistula
- Paget’s disease
- Beriberi

**Treatment**
- Determine if CHF is secondary to systolic or diastolic dysfunction and treat accordingly.
- Identify and correct precipitating factors (i.e., anemia, thyrotoxicosis, infections, ↑ sodium load, medical noncompliance).
- ↓ Cardiac workload in pts w/systolic dysfunction: restrict pt’s activity only during periods of acute decompensation.
- ↓ Na intake to <2 g/day
- ↓ Fluid intake to ≤2 L in pts w/hyponatremia
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Treatment of CHF Secondary to Systolic Dysfunction

- ACEIs
- Diuretics (furosemide)
- β-Blockers (carvedilol or metoprolol)
- ARBs in pts unable to tolerate ACEIs
- Aldosterone antagonists: low-dose spironolactone or eplerenone Rx should be considered in pts w/NYHA class III or IV who remain symptomatic despite Rx w/ACEIs and β-blockers.
- Direct vasodilating drugs (hydralazine and isosorbid): in pts who are intolerant of both ACEIs and ARBs. They should also be considered in African American pts as an add-on to standard Rx w/ACE and ARBs when there is symptomatic heart failure.
- Digitalis is of limited value in pts w/mild CHF and nl sinus rhythm. When used, it should be reserved for pts w/symptomatic NYHA class II-IV CHF. Digoxin has a narrow therapeutic window. Its beneficial effects are found w/a low dose that results in a serum concentration of approximately 0.7 ng/mL. Higher doses may be detrimental.
- ICDs: in pts w/EF <30% in NYHA class I, II, or III and an overall life expectancy >6 mo. Placement of a biventricular pacemaker is beneficial in symptomatic pts w/EF <35% and QRS interval >130 ms on ECG despite maximal medical Rx.
- Other agents: use of inotropic agents (dobutamine, milrinone) should be reserved for pts w/severe heart failure unresponsive to other Rx noted before. Use of nesiritide should be reserved for pts who present to the hospital w/acutely decompensated heart failure and dyspnea at rest in whom standard combination Rx w/diuretics and NTG has been inadequate. It should not be substituted for diuretics, used for intermittent outpatient infusion, or used repetitively.

Treatment of CHF Secondary to Diastolic Dysfunction

- The initial treatment of diastolic heart failure should be directed at ↓ the congestive state w/the use of diuretics, being careful to avoid excessive diuresis. Long-term goal is to control HTN, tachycardia, congestion, and ischemia. Rx options are determined by the cause.
- HTN: CCBs, ACEIs, β-blockers, diuretics, ARBs
- AS: aortic valve replacement in pts w/critical stenosis, diuretics
- AI, MR: ACEs, surgery
- HCM: β-blockers or verapamil. Restoration of intravascular volume w/IV saline solution if necessary in acute pulmonary edema. DDD pacing is useful in selected pts.

119 CONSTRICTIVE PERICARDITIS, CHRONIC

Definition
Fibrous scarring and adhesions of the two pericardial layers, which can obliterate the pericardial cavity and cause the pericardium to become rigid and thickened; this results in ↓ distensability in all four chambers and prevents the ventricles from adequately filling during diastole and causes ↑ venous pressures and ↓ SV.

Diagnosis

Clinical Presentation
- JVD, Kussmaul's sign (↑ in JVD during inspiration due to ↑ venous return)
- Pericardial knock (early diastolic filling sound heard 0.06-0.1 sec after S2)
- Clear lungs
- Tender hepatomegaly
- Pedal edema, ascites
- Absence of pulsus paradoxus

Differential Diagnosis
- Restrictive cardiomyopathy
- SVC obstruction
- TR w/right ventricular dysfunction
- Primary hepatic disease or nephrotic syndrome
- Right-sided CHF
Diagnostic Studies
- CXR: clear lung fields, nl or slightly enlarged heart; pericardial calcification may be seen
- ECG: low-voltage QRS complexes, nonspecific ST-T wave changes
- Echo: pericardial thickening, rapid early diastolic pressures, attenuated late diastolic filling
- Cardiac cath: equalization of right and left ventricular diastolic pressures, square-root sign, prominent y descent

Etiology
- Idiopathic
- Post-irradiation Rx
- Uremia
- Tuberculous pericarditis
- After idiopathic pericarditis
- Tumor infiltration

Treatment
- Surgical stripping and removal of both layers of the constricting pericardium

119 COR PULMONALE

Definition
Enlargement of the right ventricle and deterioration of its function secondary to diseases affecting the lungs or pulmonary vasculature that cause pulmonary HTN. Cor pulmonale may be acute or chronic.

Diagnosis

Labs
- CBC: erythrocytosis secondary to hypoxia
- ABGs: hypoxemia and acidosis or hypercapnia

Imaging
- CXR: evidence of COPD and pulmonary HTN (e.g., RA, RV, and pulmonary enlargement)
- ECG: RVH, right atrial enlargement (P pulmonale), RAD or incomplete or complete RBBB.
- Echo w/continuous, pulse, and color Doppler study can estimate PAP. M-mode and two-dimensional studies measure chamber size and wall thickness.
- Right-sided catheterization measures PAPs and vascular resistance. It also helps determine response to various Rx (e.g., oxygen, CCBs, ACEIs).

Etiology
- Pulmonary HTN (idiopathic, emphysema, ILD, pulmonary emboli)

Treatment
- Rx underlying etiology while at the same time reversing hypoxemia, hypercapnia, and acidosis. Improve RV contraction and ↓ pulmonary artery vascular resistance.

120 CORONARY ARTERY DISEASE (CAD; ANGINA, ATHEROSCLEROTIC HEART DISEASE, ASHD)

Definition
Angina pectoris is characterized by discomfort that occurs when myocardial oxygen demand exceeds the supply. Myocardial ischemia can be asymptomatic (silent ischemia), particularly in diabetics. Angina is graded in 4 classes by the Canadian Cardiovascular Society classification system:
- Class I: Ordinary physical activity (such as walking, climbing stairs) does not cause angina. Angina occurs w/strenuous, rapid, or prolonged exertion at work or recreation.
- Class II: Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing pc, in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a nl pace and in nl conditions.
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Class III: Marked limitations of ordinary physical activity. Angina occurs on walking one to two blocks on the level and climbing one flight of stairs in nl conditions and at a nl pace.

Class IV: Inability to carry on any physical activity w/o discomfort—anginal sx may be present at rest.

Diagnosis

H&P

- The most important diagnostic factor is the hx (e.g., chest pain, pressure, jaw pain, lt arm pain) (Table 3-10).
- PE: little diagnostic help and may be nl in many pts, although the presence of an S4 gallop is suggestive of ischemic chest pain.

ECG

- ECG: during the acute episode may show transient T wave inversion or ST-segment depression or elevation, but some pts may have a nl tracing.

Imaging

- Echo: indicated in pts w/systolic murmur suggestive of AS, MVP, or hypertrophic cardiomyopathy. Echo combined w/treadmill exercise (stress echo) or pharmacologic stress w/dobutamine can be used to detect regional wall abnormalities that occur during myocardial ischemia associated w/CAD.
- Cardiac cath: if + stress test result

Labs

- Cardiac troponins, CK-MB in patients presenting with symptoms suggestive of myocardial ischemia
- Lipid panel, FBS to evaluate risk factors

Etiology

Uncontrollable Risk Factors for Angina

- Advanced age
- Male sex
- Genetic predisposition

Modifiable Risk Factors for Angina

- Smoking (risk is almost double)
- HTN
- Hyperlipidemia
- Impaired fasting glucose or DM
- Obesity (weight >30% above ideal)
- Hypothyroidism
- LVH
- Sedentary lifestyle
- Oral contraceptive use
- Cocaine use
- ↑ Homocysteine levels
- ↑ Levels of highly sensitive C-reactive protein (hs-CRP, Cardio CRP)
- ↑ Levels of lipoprotein-associated phospholipase A2, ↑ fibrinogen level
- Depression
- Vasculitis

Treatment

- The major classes of anti-ischemic agents are nitrates, β-blockers, CCB, and ASA; they can be used alone or in combination. (see section on “Acute Coronary Syndrome”)
- PCI (angioplasty and coronary stents): for pts w/one- or two-vessel disease that does not involve the main left coronary artery and in whom ventricular function is nl or nearly nl.
- CABG surgery: for pts w/left main coronary disease, for those w/symptomatic three-vessel disease, and for those w/left ventricular EF <40% and critical (>70% stenosis) in all three major coronary arteries. Surgical Rx improves prognosis, particularly in diabetic pts w/multivessel disease.
- Correction of possible aggravating factors (e.g., anemia, HTN, DM, hyperlipidemia, thyrotoxicosis, hypothyroidism)
### TABLE 3-10  ■ Likelihood of Ischemic Etiology and Short-Term Risk

#### Part I. Chest pain patients without ST-segment elevation: likelihood of ischemic etiology

<table>
<thead>
<tr>
<th>A. High Likelihood</th>
<th>B. Intermediate Likelihood</th>
<th>C. Low Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>High likelihood that chest pain is of ischemic etiology if patient has <em>any</em> of the findings in the column below:</td>
<td>Intermediate likelihood that chest pain is of ischemic etiology if patient has <em>no</em> findings in column A and <em>any</em> of the findings in the column below:</td>
<td>Low likelihood that chest pain is of ischemic etiology if patient has <em>no</em> findings in column A or B. Patients may have any of the findings in the column below:</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td><strong>History</strong></td>
<td><strong>History</strong></td>
</tr>
<tr>
<td>Chief symptom is chest or left arm pain or discomfort <em>plus</em></td>
<td>Chief symptom is chest or left arm pain or discomfort Age &gt;70 yr Male sex Diabetes mellitus</td>
<td>Probably ischemic symptoms Recent cocaine use</td>
</tr>
<tr>
<td>Current pain reproduces pain of previous documented angina and known CAD, including MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical exam</strong></td>
<td><strong>Physical exam</strong></td>
<td><strong>Physical exam</strong></td>
</tr>
<tr>
<td>Transient mitral regurgitation Hypotension Diaphoresis Pulmonary edema or rales</td>
<td>Extracardiac vascular disease</td>
<td>Chest discomfort reproduced by palpation</td>
</tr>
<tr>
<td><strong>ECG</strong></td>
<td><strong>ECG</strong></td>
<td><strong>ECG</strong></td>
</tr>
<tr>
<td>New (or presumed new) transient ST deviation (≥0.5 mm) or T wave inversion (≥2 mm) with symptoms</td>
<td>Fixed Q waves Abnormal ST segments or T waves that are not new</td>
<td>Normal ECG or T wave flattening or T wave inversion in leads with dominant R waves</td>
</tr>
<tr>
<td><strong>Cardiac markers</strong></td>
<td><strong>Cardiac markers</strong></td>
<td><strong>Cardiac markers</strong></td>
</tr>
<tr>
<td>Elevated troponin I or T Elevated CK-MB</td>
<td><em>Any finding in column B above plus</em> Normal cardiac markers</td>
<td>Normal cardiac markers</td>
</tr>
</tbody>
</table>

#### Part II. Risk of death or nonfatal MI during the short term in patients with chest pain with high or intermediate likelihood of ischemia (columns A and B in Part I)

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk is high if patient has <em>any</em> of the following findings:</td>
<td>Risk is intermediate if patient has <em>any</em> of the following findings:</td>
<td>Risk is low if patient has <em>no</em> high- or intermediate-risk features; may have any of the following:</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td><strong>History</strong></td>
<td><strong>History</strong></td>
</tr>
<tr>
<td>Accelerating tempo of ischemic symptoms during previous 48 hours</td>
<td>Prior MI or Peripheral artery disease or Cerebrovascular disease or CABG, previous aspirin use</td>
<td></td>
</tr>
<tr>
<td><strong>Character of pain</strong></td>
<td><strong>Character of pain</strong></td>
<td><strong>Character of pain</strong></td>
</tr>
<tr>
<td>Prolonged, continuing (&gt;20 min) rest pain</td>
<td>Prolonged (&gt;20 min) rest angina is now resolved (moderate to high likelihood of CAD) Rest angina (&lt;20 min) or relieved by rest or sublingual nitrates</td>
<td>New-onset functional angina (class III or IV) in past 2 wk without prolonged rest pain (but with moderate or high likelihood of CAD)</td>
</tr>
</tbody>
</table>
TABLE 3-10  **Likelihood of Ischemic Etiology and Short-Term Risk—cont’d**

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary edema secondary to ischemia</td>
<td>Age &gt;70 yr</td>
<td></td>
</tr>
<tr>
<td>New or worse mitral regurgitation murmur</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension, bradycardia, tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S₂ gallop or new or worsening rales</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ST deviation (≥0.5 mm) with rest angina</td>
<td>T wave inversion ≥2 mm</td>
<td>Normal or unchanged ECG during an episode of chest discomfort</td>
</tr>
<tr>
<td>New or presumably new BBB</td>
<td>Pathologic Q waves or T waves that are not new</td>
<td></td>
</tr>
<tr>
<td>Sustained VT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac markers</td>
<td><strong>Any of the above findings plus</strong></td>
<td><strong>Normal cardiac markers</strong></td>
</tr>
<tr>
<td>Elevated cardiac troponin I or T</td>
<td>Normal cardiac markers</td>
<td></td>
</tr>
<tr>
<td>Elevated CK-MB</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Prevention**
- Smoking cessation
- BP control (<140/90 mm Hg, <130/80 mm Hg in diabetics or renal disease)
- Lipid management (LDL <70 mg/dL)
- Exercise (30 min at least 5 days/wk); weight loss if overweight (keep BMI 18.5-24.9); waist circumference <40 inches in men, <35 inches in women
- Antiplatelet Rx: ASA 75-162 mg
- β-Blockers (unless contraindicated)

**Clinical Pearl**
- Within 12 mo of initial dx, 10%-20% of pts w/dx of stable angina progress to MI or unstable angina.

**CROHN’S DISEASE**

**Definition**
Inflammatory disease of the bowel most commonly involving the terminal ileum and manifesting primarily w/diarrhea, abd pain, fatigue, and weight loss.

**Diagnosis**

**H&P**
- Abd tenderness, mass, or distention
- Chronic or nocturnal diarrhea
- Weight loss, fever, night sweats
- Hyperactive bowel sounds in pts w/partial obstruction, bloody diarrhea
- Delayed growth and failure of nl development in children
- Perianal and rectal abscesses, mouth ulcers, and atrophic glossitis
- Extraintestinal manifestations: joint swelling and tenderness, hepatosplenomegaly, erythema nodosum, clubbing, tenderness to palpation of the sacroiliac joints
- Sx may be intermittent w/varying periods of remission.

**Labs**
- ↓ Hgb/Hct from chronic blood loss, effect of inflammation on bone marrow, and malabsorption of vitamin B₁₂
- ↓ K, Mg, Ca, alb in pts w/chronic diarrhea
- Vitamin B₁₂ and folate deficiency
- ↑ ESR, +ASCA, –ANCA
Imaging
- Endoscopic features of Crohn’s disease include asymmetric and discontinued disease, deep longitudinal fissures, cobblestone appearance, presence of strictures. Crypt distortion and inflammation are also present. Granulomas may be present.
- Barium imaging studies (when performed) reveal deep ulcerations (often longitudinal and transverse) and segmental lesions (skip lesions, strictures, fistulas, cobblestone appearance of mucosa caused by submucosal inflammation); “thumbprinting” is common; “string sign” in terminal ileum may be noted.
- CT abd: helpful in identifying abscesses and other complications
- In 5%-10% of pts w/IBD, a clear distinction between UC and Crohn’s disease cannot be made. In general, Crohn’s disease can be distinguished from UC by transmural involvement and the frequent presence of noncaseating granulomas and lymphoid aggregates on bx.

Treatment
- Sulfasalazine, 500 mg PO qid initially, ↑ qd or qod by 1 g until therapeutic dosages of 4-6 g/day are achieved. The oral salicylates (mesalamine [Asacol, Rowasa]) are as effective as sulfasalazine and better tolerated but more expensive; they may be useful in pts allergic to the sulfa moiety of sulfasalazine molecule. Individuals w/sulfa allergies should avoid sulfasalazine. Folate supplementation is recommended because sulfasalazine inhibits folate absorption.
- Corticosteroids: Prednisone 40-60 mg/day is useful for acute exacerbation. Steroids are usually tapered during approximately 2-3 mo. Some pts require a low dose for prolonged period of maintenance.
- Steroid analogues are locally active corticosteroids that target specific areas of inflammation in the GI tract. Budesonide is available as a controlled-release formulation and is approved for mild to moderately active Crohn’s disease involving the ileum or ascending colon. The adult dose is 9 mg qd for a maximum of 8 wk.
- Immunosuppressants (azathioprine, MTX, cyclosporine): used for severe, progressive disease.
- Metronidazole: useful for colonic fistulas and for treatment of mild to moderately active Crohn’s disease. Ciprofloxacin 1 g qd has also been found effective in ↓ disease activity.
- Infliximab: effective in the treatment of enterocutaneous fistulas. Natalizumab and adalimumab are also effective in inducing remissions.
- Hydrocortisone enema: useful for proctitis.
- Erythropoietin: useful in pts w/anemia refractory to treatment w/iron and vitamins.
- Nutritional supplementation: in pts w/advanced disease. TPN may be necessary in selected pts.
- Low-residue diet is necessary when obstructive sx are present.
- If diarrhea is prominent, ↑ dietary fiber and ↓ of fat in the diet.
- Psychotherapy is useful for situational adjustment crises. A trusting and mutually understanding relationship and referral to self-help groups are important because of the chronicity of the disease and the relatively young age of the pts.

Clinical Pearl
- 10% have prolonged remission, 75% have a chronic intermittent disease course, and 12% have an unremitting course.

122 CRYOGLOBULIN SYNDROMES

Definition
Presence in the serum of one or more immunoglobulins that reversibly precipitate at temperatures <37°C. It is traditionally classified into 3 subgroups:
- Type I, composed of single monoclonal immunoglobulin: found mainly in pts w/overt lymphoid tumors (e.g., lymphocytotplasmic lymphoma, Waldenström’s macroglobulinemia, MM). It is generally asymptomatic but in a few cases can be complicated by hyperviscosity syndrome.
Type II and type III mixed cryoglobulinemias, immune complexes composed of polyclonal IgG (the autoantigens) and monoclonal or polyclonal IgMs, respectively. These may be associated w/various infectious, immunologic, or neoplastic diseases.

**Diagnosis**
- Cutaneous manifestations of mixed cryoglobulinemia are the most frequent sx of the disease. Orthostatic purpura is usually intermittent, and the dimension and dissemination of skin lesions vary widely from sporadic, isolated petechiae to severe vasculitic lesions, often complicated by ulcers of the legs and malleolar areas.

**Treatment**
- Rx of underlying disease in type I cryoglobulinemia
- Hyperviscosity syndrome may require plasma exchange.

**Clinical Pearl**
- Rituximab and the combination of prednisolone and the Japanese immunosuppressive reagent mizoribine may be effective in selected pts.

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**CRYPTOCOCCOSIS**

**Definition**
Infection caused by the fungal organism *Cryptococcus neoformans*.

**Diagnosis**

**H&P**
- >90% present w/meningitis; almost all have fever and headache.
- Meningismus, photophobia, ΔMS are seen in approximately 25%.
- Most common infections outside the CNS:
  - Lungs (fever, cough, dyspnea)
  - Skin (cellulitis, papular eruption)
  - Lymph nodes (lymphadenitis)

**Labs**
- Culture and India ink stain (60%-80% sensitive in culture-proven cases), examination of the CSF in all cases when CNS involvement is suspected
- Blood and serum cryptococcal antigen assay (>90% sensitivity and specificity)
- Culture and histologic examination of bx material
- HIV

**Imaging**
- CT scan or MRI of the head: if focal neurologic involvement is suspected
- CXR: to exclude pulmonary involvement

**Etiology**
- Caused by the fungal organism *C. neoformans*
- Transmission almost always in the setting of AIDS or other disorders of cellular immune function (hematologic malignant neoplasms, long-term corticosteroid Rx, immunosuppressive Rx after organ transplantation), or pregnancy

**Treatment**
- Rx w/IV amphotericin B (0.8 mg/kg/day) w/flucytosine 37.5 mg/kg
- After stabilization (usually several weeks), consider fluconazole (200-400 mg qd PO) for additional 6-8 wk. Voriconazole, a newer imidazole, also has activity against most isolates.
- Alternative: IV fluconazole for initial Rx in pts unable to tolerate amphotericin B
- If symptomatic ↑ ICP: therapeutic LP or intraventricular shunt

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**CRYPTOSPORIDIOSIS**

**Definition**
Infection w/the intracellular protozoan parasite *Cryptosporidium parvum*. 


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**CUSHING’S SYNDROME**

**Definition**
Clinical disorder associated w/glucocorticoid excess secondary to exaggerated adrenal cortisol production or chronic glucocorticoid Rx. *Cushing’s disease* is Cushing’s syndrome caused by pituitary ACTH excess.

**Diagnosis**

**H&P**
- HTN
- Central obesity w/rounding of the facies (*moon facies*); thin extremities
- Hirsutism, menstrual irregularities, hypogonadism
- Skin fragility, ecchymoses, red-purple abd striae, acne, poor wound healing, hair loss, facial plethora, hyperpigmentation (when there is ACTH excess)
- Psychosis, emotional lability, paranoia
- Muscle wasting w/proximal myopathy

**Labs**
- Initial screening test is the overnight dexamethasone suppression test (Fig. 3-17):
  - Dexamethasone 1 mg PO given at 11 PM
  - Plasma cortisol level measured 9 hr later (8 AM)
  - Plasma cortisol level <5 µg/100 mL excludes Cushing’s syndrome
- Serial measurements (2-3 consecutive measurements) of 24-hr urinary free cortisol and Cr (to ensure adequacy of collection) are undertaken if overnight dexamethasone test result is suggestive of Cushing’s syndrome. Persistent ↑ cortisol excretion (>300 µg/24 hr) indicates Cushing’s syndrome.
- The low-dose (2 mg) dexamethasone suppression test is useful to exclude pseudo-Cushing’s syndrome if the results are equivocal. CRH stimulation after low-dose dexamethasone administration (dexamethasone-CRH test) is also used to distinguish pts w/suspected Cushing’s syndrome from those who have mildly ↑ urinary free cortisol level and equivocal findings.
- A single midnight serum cortisol concentration (nl diurnal variation leads to a nadir around midnight) >7.5 µg/dL has been reported as 96% sensitive and 100% specific for the dx of Cushing’s syndrome.
- Other lab tests reveal: hypokalemia, hypocloremia, metabolic alkalosis, hyperglycemia, hypercholesterolemia, ↑ 24-hr urinary free cortisol (>100 µg/24 hr)
**Imaging**
- CT scan of adrenal glands: indicated in suspected adrenal Cushing’s syndrome
- MRI of pituitary gland w/gadolinium: indicated in suspected pituitary Cushing’s syndrome

**Etiology**
- Iatrogenic from chronic glucocorticoid Rx (most common) (↓ ACTH, ↑ cortisol)
- Pituitary ACTH excess (Cushing’s disease) (↑ ACTH, ↑ cortisol)
- Adrenal neoplasms (30%) (↓ ACTH, ↑ cortisol)
- Ectopic ACTH production (neoplasms of lung, pancreas, kidney, thyroid, thymus; 10%) (↑↑ ACTH, ↑↑ cortisol)

**Treatment**
Treatment varies w/cause:
- Pituitary adenoma: transsphenoidal microadenomectomy is the Rx of choice in adults. Pituitary irradiation is reserved for pts not cured by transsphenoidal surgery. In children, pituitary irradiation may be considered initial Rx because 85% of children are cured by radiation. Stereotactic radiotherapy (photon knife or gamma knife) is effective and exposes the surrounding neuronal tissues to less irradiation than in conventional radiotherapy. Total bilateral adrenalectomy is reserved for pts not cured by transsphenoidal surgery or pituitary irradiation.
- Adrenal neoplasm: surgical resection of the affected adrenal; glucocorticoid replacement for approximately 9-12 mo after the surgery to allow time for the contralateral adrenal to recover from its prolonged suppression
- Bilateral micronodular or macronodular adrenal hyperplasia: bilateral total adrenalectomy
- Ectopic ACTH: surgical resection of the ACTH-secreting neoplasm; control of cortisol excess w/metyrapone, aminoglutethimide, mifepristone, or ketoconazole; control of the mineralocorticoid effects of cortisol and 11-deoxycorticosteroid w/spironolactone. Bilateral adrenalectomy is a rational approach to pts w/indolent, unresectable tumors.

**Clinical Pearls**
- In Cushing’s syndrome secondary to ectopic ACTH production, many of these tumors secrete a biologically inactive ACTH that does not activate adrenal steroid synthesis. These pts may have only weight loss and weakness.
- Screening for MEN I should be considered in pts w/Cushing’s disease.

**Figure 3-17.** Diagnostic algorithm for Cushing’s syndrome.
126 CYSTIC FIBROSIS (CF)

Definition
Autosomal recessive disorder characterized by dysfunction of exocrine glands. More prevalent in northern and central Europeans.

Diagnosis
- A dx of CF requires a positive result of quantitative pilocarpine iontophoresis test w/one or more phenotypic features consistent w/CF (e.g., chronic suppurative obstructive lung disease, pancreatic insufficiency) or documented CF in a sibling or first cousin.

Labs
- Pilocarpine iontophoresis (sweat test): diagnostic of CF in children if sweat chloride is >60 mmol/L (>80 mmol/L in adults) on two separate tests on consecutive days
- DNA testing may be useful for confirming the dx and providing genetic information for family members.
- Sputum C&S and Gram stain (frequent bacterial infections w/S. aureus, Pseudomonas, H. influenzae)
- ↓ Alb level, ↑ 72-hr fecal fat excretion
- ABGs or pulse oxymetry: hypoxemia
- PFTs: ↓ TLC, FVC, pulmonary diffusing capacity

Imaging
- CXR: focal atelectasis, peribronchial cuffing, bronchiectasis, ↑ interstitial markings, hyperinflation
- High-resolution chest CT: bronchial wall thickening, cystic lesions, ring shadows (bronchiectasis)

Etiology
- Chromosome 7 gene mutation (CFTR gene) resulting in abnormalities in chloride transport and water flux across the surface of epithelial cells. The abnl secretions cause obstruction of glands and ducts in various organs and subsequent damage to exocrine tissue (recurrent pneumonia, atelectasis, bronchiectasis, DM, biliary cirrhosis, cholelithiasis, intestinal obstruction, ↑ risk of GI malignant neoplasms).

Treatment
- Postural drainage and chest percussion
- Encouragement of regular exercise and proper nutrition
- Abx Rx based on results of Gram stain and C&S of sputum (PO ciprofloxacin or floxacinil for Pseudomonas, ceps for S. aureus, IV AGs plus ceftazidime for life-threatening Pseudomonas infections). Macrolides are also active against Pseudomonas aeruginosa. Azithromycin maintenance in children w/CF may be beneficial.
- Bronchodilators for pts w/airflow obstruction
- Chronic pancreatic enzyme replacement
- Alternate-day prednisone (2 mg/kg) possibly beneficial in children w/CF (↓ hospitalization rate, improved pulmonary function); routine use of corticosteroids not recommended in adults; among children w/CF who have received alternate-day treatment w/prednisone, boys but not girls have persistent growth impairment after treatment is discontinued.
- Proper nutrition and vitamin supplementation.
- Recombinant human deoxyribonuclease (DNase [dornase alfa]) 2.5 mg qd or bid given by aerosol for pts w/viscid sputum. It is useful to improve mucociliary clearance by liquefying difficult-to-clear pulmonary secretions. It is, however, very expensive. Its cost can be ↓ by using alternate-day rhDNase Rx.
- Intermittent administration of inhaled tobramycin has been reported beneficial in CF.
- Treatment of hyperglycemia and DM
- Pneumococcal vaccination, yearly influenza vaccination
- Lung transplantation is the only definitive treatment; 3-yr survival after transplantation >50%.
Clinical Pearl
- Genetic testing for CF should be offered to adults w/positive FHx of CF, to couples currently planning a pregnancy, and to couples seeking prenatal care.
- Suspect dx in children with nasal polyps, meconium ileus in newborns, failure to clear mucus secretions.

127 CYTOMEGALOVIRUS (CMV RETINITIS)
Definition
Infection w/CMV, a herpes virus.

Diagnosis
H&P
- Funduscopic: necrotic patches w/white granular component of retina

Labs
- Demonstration of virus in tissue or serologic testing including CMV IgM Abs, rising titers of complement fixation and indirect fluorescent antibody (IFA) or anticomplement IFA
- Cultures (viral): human fibroblast from urine, cervical swab, tissue buffy coat
- Bx: “owl’s eye” inclusion bodies on tissue sample

Treatment
- HAART in pts w/CD4 count <50/mm³ for the goal of CD4 >100/mm³ for a 3- to 6-mo period
- For compromised hosts w/CMV retinitis or pneumonitis:
  - Ganciclovir 5 mg/kg bid IV × 14-21 days, then 5 mg/kg/day IV, or 1 g PO tid or ocular implant
  - Foscarnet 60 mg/kg tid × 3 wk, then 90 mg/kg/day
  - Cidofovir 5 mg/kg IV, repeat 1 wk later, then q2wk IV
  - Fomivirsen: salvage Rx for CMV retinitis, 300 µg injected into vitreous

128 DECUBITUS ULCERS (PRESSURE ULCERS)
Definition
Damage to the skin and the underlying tissue or both from pressure, friction, or shearing forces that usually occur over bone prominences.

Staging
All pressure ulcers should be staged according to depth and type of tissue damage. A new pressure staging system was developed in 2007, adding the last 2 stages:
- Stage I: nonblanchable erythema of intact skin or boggy, mushy feeling of skin
- Stage II: partial-thickness skin loss involving the epidermis, dermis, or both
- Stage III: full-thickness skin loss involving damage or necrosis of SC tissue that may extend down to but not through underlying fascia or muscle
- Stage IV: full-thickness skin loss w/extensive destruction and tissue damage to muscle, bone, or supporting structures (e.g., tendons, joint capsule)
- Deep tissue injury: purple or maroon skin overlying an area of dead tissue (muscle or fat), which will later develop into a stage III or IV ulcer
- Unstageable: ulcer base is covered by slough and eschar and cannot be staged

Diagnosis
Labs
- Directed at identifying cause of risk factors or any complications arising from the pressure ulcer (e.g., abscess or osteomyelitis)
- Cultures of wound bed are not helpful and should not be performed.
- ↓ Alb levels may reveal malnutrition.
- CBC if infection is suspected

Imaging
- MRI: may help identify osteomyelitis when clinically suspected
Etiology

Decubitus ulcers are caused by constant, unrelieved pressure in tissues where circulation is ↓, leading to necrosis of the tissues. Shearing and friction forces can also contribute or cause damage to the tissues, leading to an ulcer.

Treatment

Area involved should be cleaned at each dressing change; necrotic tissue should be debrided quickly as it delays wound healing.

Wound irrigation should not exceed 15 psi and is best done w/an 18-gauge angiocatheter.

No one dressing or product is superior; should be used to keep ulcer bed moist and protect it from urine and stool.

Avoid agents that are cytotoxic to epithelial cells (e.g., iodine, iodophor, sodium hypochlorite, hydrogen peroxide, acetic acid, and alcohol).

Pressure by using foam mattress, dynamic support surface (e.g., low-air-loss bed), and frequent repositioning (e.g., q2h).

Hyperbaric oxygen, U/S, ultraviolet and low-energy radiation either are ineffective or have not been extensively evaluated for efficacy.

Negative-pressure devices (VAC devices) may help for wounds that have significant drainage.

Correct poor nutrition.

Minimize urinary and fecal incontinence.

Use standardized assessment tool (e.g., PUSH tool) to monitor wound healing on weekly basis.

No benefit was found w/nutritional supplements or U/S Rx.

Pain medications may be necessary as 50% of decubitus ulcers are painful.

Growth factors appear promising but are second-line treatments if traditional approaches are ineffective.

129 DEEP VENOUS THROMBOSIS (DVT)

Definition

Presence of thrombi in the deep veins of the extremities or pelvis.

Diagnosis

H&P

- Pain and swelling of the affected extremity
- In LE DVT: leg pain on dorsiflexion of the foot (Homans’ sign)
- Exam may be unremarkable in early DVT.
- Clinical prediction rules can be used to establish pretest probability of DVT. The Wells’ prediction rules for DVT and for PE are described in Table 3-11. These rules perform better in younger pts w/o h/o DVT and in those w/o comorbidities. In younger pts w/o associated comorbidities and a low pretest probability by Wells’ criteria and a negative high-sensitivity D-dimer test result, the dx of DVT can be reasonably excluded.

<table>
<thead>
<tr>
<th>TABLE 3-11</th>
<th>Wells’ Clinical Assessment Model for the Pretest Probability of Lower Extremity DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing or within previous 6 months or palliative)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden &gt;3 days or major surgery within 4 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling &gt;3 cm asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis as likely as or greater than that of DVT</td>
<td>–2</td>
</tr>
</tbody>
</table>

In patients with symptoms in both legs, the more symptomatic leg is used. Pretest probability is calculated as the total score: high, >3; moderate, 1-2; low, <0.
Labs
- Baseline PT (INR), APTT, and platelet count should be obtained on all pts before anticoagulation is started.
- D-dimer assay by ELISA: DVT can be ruled out in pts who are clinically unlikely to have DVT and have a negative D-dimer test result. D-dimer can also be combined w/U/S. The combination of a nl D-dimer w/ nl compression venous U/S is useful to exclude DVT and to eliminate the need for repeated U/S at 5-7 days. Figure 3-18 is an algorithm for the diagnosis of DVT.
- R/o hypercoagulable state: young pts w/DVT, pts w/recurrent thrombosis w/o obvious causes, and those w/FHx of thrombosis. Labs should include protein S, protein C, fibrinogen, antithrombin III level, lupus anticoagulant, ACLs, factor V Leiden, factor VIII, factor IX, and plasma homocysteine levels.

Imaging
- Compression U/S: preferred as the initial study to dx DVT. An initially normal test, in absence of D-dimer, should be repeated after 5 days (if the clinical suspicion of DVT persists) to detect propagation of any thrombosis to the proximal veins.

Etiology
The etiology is often multifactorial (prolonged stasis, coagulation abnormalities, vessel wall trauma). The following are risk factors for DVT:
- Prolonged immobilization (≥3 days)
- Postop
- Trauma to pelvis and LEs for LE DVT; central line placement for UE DVT
- Birth control pills, high-dose estrogen Rx; conjugated equine estrogen but not esterified estrogen is associated w/↑ risk of DVT; estrogen + progestin is associated w/doubling of the risk of venous thrombosis.
Visceral cancer (lung, pancreas, alimentary tract, GU tract)
Age >60 yr
H/o thromboembolic disease
Hematologic disorders (e.g., factor V Leiden [FVL] mutation, antithrombin III deficiency, protein C deficiency, protein S deficiency, heparin cofactor II deficiency, sticky platelet syndrome, G20210A prothrombin mutation, lupus anticoagulant, dysfibrinogenemias, ACL, hyperhomocysteinemia, concurrent homocystinuria, high levels of factors VIII and XI, and single nucleotide polymorphisms such as CYP4V2)
Pregnancy and early puerperium
Obesity (BMI >30)
CHF
Surgery, fx, or injury involving lower leg or pelvis
Surgery requiring >30 min of anesthesia
Gyn surgery (particularly gyn cancer surgery)
Recent travel (within 2 wk, lasting >8 hr)
Smoking and Abd obesity
Central venous catheter or pacemaker insertion
Superficial vein thrombosis, varicose veins
Long-term exposure to particulate air pollution is associated w/ altered coagulation function and DVT risk.

Treatment
LMWH for 4-7 days followed by PO warfarin. Recommended dose of enoxaparin is 1 mg/kg q12h SC and continued for a minimum of 5 days and until a therapeutic INR (2-3) has been achieved w/warfarin. Warfarin Rx should be initiated when appropriate (usually within 72 hr of initiation of heparin).
Long-term LMWH may be preferable to warfarin in pts w/cancer or those whose INR is difficult to control.
Outpatient treatment of DVT is appropriate for pts w/o prior DVT, thrombophilic conditions, or substantial comorbidity, but not for those who are pregnant or likely not to adhere to Rx.
Exclusions from outpatient treatment of DVT include pts w/potential high complication risk (e.g., Hgb <7, platelet count <75,000, guaiac-positive stool, recent CVA or noncutaneous surgery, noncompliance).
Compression stockings are effective in ↓ the incidence of post-thrombotic syndrome and should be started within 1 mo of proximal DVT and used for at least 1 yr after dx.
Insertion of an IVC filter to prevent PE is recommended in pts w/ contraindications to anticoagulation.
Thrombolytic Rx (streptokinase) can be used in rare cases (unless contraindicated) in pts w/extensive iliofemoral venous thrombosis and a low risk of bleeding.
Pharmacomechanical catheter directed thrombolysis (PCDT) is a newer treatment modality.

Clinical Pearls
When heparin is used, there is a risk of HIT (w/unfractionated more so than w/LMWH). Platelet count should be obtained initially and repeated q 3 days while on heparin.
The optimal duration of anticoagulant Rx varies w/the cause of DVT and risk factors:
- Rx for 3-6 mo: pts w/reversible risk factors (low-risk group). ↑ D-dimer level measured after 3 mo of anticoagulation in pts w/unprovoked DVT should favor a longer duration of Rx.
- Anticoagulation for at least 6 mo: pts w/idopathic venous thrombosis or medical risk factors for DVT (intermediate-risk group).
- Indefinite anticoagulation: pts w/DVT associated w/active cancer; pts w/inherited thrombophilia (e.g., deficiency of protein C or S Ab), antiphospholipid, and recurrent episodes of idiopathic DVT (high-risk group).
Measurement of D-dimer after withdrawal of oral anticoagulation may be useful to estimate the risk of recurrence. Pts w/a first spontaneous DVT and a D-dimer level <250 mg/mL after withdrawal of oral anticoagulation have a ↓ risk of DVT recurrence.

130 DELIRIUM AND DEMENTIA

Diagnosis
- Delirium is mainly differentiated from dementia by the hx: short onset within hours to a few weeks w/a waxing and waning quality favors delirium, whereas chronic disturbance or gradual onset favors dementia. The hx must be substantiated by the caregivers.
- The elderly person whose clinical presentation suggests neuromuscular or mental derangement, whether chronic or acute, must be evaluated as if he/she had a diagnostic state of delirium.
- Physical abnormalities or dysfunctions can have an impact on cognitive and neuromuscular function and disrupt psychiatric homeostasis; systemic and metabolic abnormalities must be r/o w/thorough H&P and labs.
- Risk factors for delirium are advanced age, preexisting cognitive deficit, prior episode of delirium, polypharmacy, alcohol or other drug dependence, use of psychoactive drugs (benzos, anticholinergics, narcotics), deficits in vision or hearing, perioperative complications, immobility, and severe comorbidity.
- The diagnostic evaluation should include the following:
  - An attempt at the Folstein Mini-Mental State Examination or mini-cog exam (see Section 1) to screen for dementia and to document the progression of disease over time by repeating the test at 3- to 6-mo intervals.
  - One venipuncture for a profile of blood values: glucose, CBC, lytes, ALT, AST, BUN, Cr, VDRL, Ca, Mg, TSH, HIV (selected pts), B_12_ level, RBC folate
  - Depending on PE and hx findings, other tests may include CT scan of head and LP. When no obvious cause is revealed from these steps, further targeted evaluation in selected pts may include toxicology screen, ammonia level, and cortisol level. EEG is useful only in diagnosing occult seizure disorder and differentiating delirium from nonorganic psychiatric disorders.
- Of great importance is the identification of treatable causes of dementia:
  - Drug induced
  - Depression
  - Hypothyroidism
  - Hyperthyroidism
  - Hypoglycemia
  - Vitamin B_12_ or folate deficiency
  - Subdural hematoma
  - Liver failure
  - NPH
  - Stroke
  - CNS infections
  - Other infection
  - Cerebral neoplasm
  - Renal failure
  - Ethanol abuse
  - Hypoxia
  - Hypercalcemia
  - Vasculitis
  - Cardiopulmonary disorders
  - Severe anemia
- Table 3-12 describes distinguishing features of common progressive dementias.
### TABLE 3-12 Distinguishing Features of Common Progressive Dementias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptoms and Signs</th>
<th>Age Affected</th>
<th>Duration of Illness</th>
<th>Neurologic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Amnestic memory loss early Getting lost Lack of awareness of one’s illness Sleep-wake cycle disturbance Apathy</td>
<td>&gt;65 yr</td>
<td>Years, up to a decade</td>
<td>Normal until advanced stage</td>
</tr>
<tr>
<td>Familial Alzheimer’s disease</td>
<td>Same as Alzheimer’s disease</td>
<td>From the 30s</td>
<td>Years</td>
<td>Normal until advanced stage</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>Personality change Disinhibition Obsessions and compulsions “Alien stare” Amnestic memory loss later Visuospatial intact</td>
<td>45-65 yr</td>
<td>Years</td>
<td>Normal until advanced stage</td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td>Early falls Visual hallucinations Neuroleptic sensitivity Fluctuating course</td>
<td>&gt;50 yr</td>
<td>Months to years</td>
<td>Early extrapyramidal signs, with rigidity greater than tremor</td>
</tr>
<tr>
<td>Corticobasal ganglionic degeneration</td>
<td>Limb apraxia “Alien hand” Visual spatial deficits</td>
<td>&gt;60 yr</td>
<td>Years</td>
<td>Apraxia Rigidity Myoclonus</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Retrieval memory loss Depression Slowness Stepwise progression</td>
<td>&gt;65 yr</td>
<td>Years</td>
<td>Focal neurologic deficits Rigidity and cogwheeling Gait abnormality</td>
</tr>
<tr>
<td>Normal-pressure hydrocephalus</td>
<td>Retrieval memory loss Urinary incontinence Progressive gait difficulty Slowness Visuospatial infarct</td>
<td>Any age</td>
<td>Months</td>
<td>Gait abnormality Hyperreflexia (legs &gt; arms) Babinski’s signs</td>
</tr>
</tbody>
</table>

**Etiology**
- **Box 3-2**

**Treatment**
- Pursue the causes.
- Avoid restraints, but use them for safety if necessary.
- Control hyperactivity of delirium w/haloperidol. Administer 0.5-1 mg IM, IV, or PO initially and observe pt for 20-30 min. If the pt remains unmanageable but has not had any adverse reactions to haloperidol, double the dose and continue monitoring. Lorazepam 1 mg IM qh may also be administered if needed, but it often has a paradoxical effect in the elderly.
- Neuropsychiatric sx of dementia are common and associated w/poor outcomes for pts and caregivers. Nonpharmacologic interventions include counseling the caregiver about the unintentional nature of the psychotic features, behavior modification, maintenance of routines, and environmental safety. Effective medications for chronic use in pts w/behavioral problems associated w/dementia are risperidone and olanzapine.
Donepezil (Aricept), rivastigmine (Exelon), and galantamine (Reminyl) are reversible acetylcholinesterase inhibitors approved for treatment of mild to moderate dementia of Alzheimer’s type. They may be helpful in delaying the progression of Alzheimer’s disease if used in the early stages. They can provide modest improvement of sx and temporary stabilization of cognition, lengthening the time from assisted community living to nursing home placement. They are, however, expensive and not recommended for pts w/advanced dementia. Memantine (Namenda) is an N-methyl-D-aspartate (NMDA) receptor blocker indicated for the treatment of moderate to severe Alzheimer’s disease. It can produce slight improvements in cognitive performance. The clinical significance of these improvements is small, and the medication is expensive. Memantine can be used in combination w/anticholinesterase inhibitors.
**DIABETES INSIPIDUS (DI)**

**Definition**
Polyuric disorder resulting from insufficient production of ADH (pituitary [neurogenic] DI) or unresponsiveness of the renal tubules to ADH (nephrogenic DI).

**Diagnosis**

**H&P**
- Polyuria: urinary volumes ranging from 2.5-6 L/day
- Polydipsia (predilection for cold or iced drinks)
- Neurologic manifestations (seizures, headaches, visual field defects)
- Evidence of volume contractions

**NOTE:** These physical findings and clinical manifestations are generally not evident until vasopressin secretory capacity is ↓ <20% of nl.

**Labs**
- ↓ Urine specific gravity (<1.005)
- ↓ Urine osmolarity (usually <200 mOsm/kg) even in the presence of high serum osmolality
- Hypernatremia, ↑ plasma osmolarity, hypercalcemia, hypokalemia

**Imaging**
- MRI of the brain if neurogenic DI is confirmed

**Etiology**

**Neurogenic Diabetes Insipidus**
- Idiopathic
- Neoplasms of brain or pituitary fossa (cranioopharyngiomas, metastatic neoplasms from breast or lung)
- Post-therapeutic neurosurgical procedures (e.g., hypophysectomy)
- Head trauma (e.g., basal skull Fx)
- Granulomatous disorders (sarcoidosis or TB)
- Histiocytosis (Hand-Schüller-Christian disease, eosinophilic granuloma)
- Familial (autosomal dominant)
- Other: interventricular hemorrhage, aneurysms, meningitis, postencephalitis, MS

**Nephrogenic Diabetes Insipidus**
- Drugs: lithium, amphotericin B, demeclocycline, methoxyflurane anesthesia
- Familial: X-linked
- Metabolic: hypercalcemia or hypokalemia
- Other: sarcoidosis, amyloidosis, pyelonephritis, polycystic disease, sickle cell disease, postobstructive

**Treatment**

**Neurogenic Diabetes Insipidus**
- Desmopressin acetate (DDAVP) 10-40 µg qd intranasally in 1-3 divided doses or in tablet form 0.05 mg bid. Usual oral dose is 0.1-1.2 mg/day in 2-3 divided doses. Desmopressin is also available in injectable form given as 2-4 µg/day SC or IV in 2 divided doses.
- Vasopressin tannate in oil: 2.5-5 U IM q24-72h; useful for long-term management because of its long life.
- In mild cases of neurogenic DI, the polyuria may be controlled w/ hydrochlorothiazide 50 mg qd.

**Nephrogenic Diabetes Insipidus**
- Adequate hydration
- Low-sodium diet and chlorothiazide to induce mild sodium depletion
- Amiloride 5 mg PO bid initially

**DIABETES MELLITUS (DM)**

**Definition**
The American Diabetes Association (ADA) defines DM as (1) a fasting plasma glucose concentration ≥126 mg/dL, (2) a nonfasting plasma glucose concentration ≥200 mg/dL, or (3) an oral glucose tolerance test value ≥200 mg/dL in the 2-hr sample. Furthermore, the ADA also defines a value of 100 mg/dL on FBS as the upper limit of nl for glucose. A fasting glucose concentration between 100 and 126 mg/dL is classified as impaired fasting glucose. When results of
Table 3-13: General Comparison of the Two Most Common Types of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous terminology</td>
<td>Insulin-dependent diabetes mellitus (IDDM), type I, juvenile-onset diabetes</td>
</tr>
<tr>
<td>Age at onset</td>
<td>Non–insulin-dependent diabetes mellitus, type II, adult-onset diabetes</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>Moderate; environmental factors required for expression; 35%-50% concordance in monozygotic twins; several candidate genes proposed</td>
</tr>
<tr>
<td>Human leukocyte antigen associations</td>
<td>Linkage to DOA and DOB, influenced by DRB (3 and 4) (DR2 protective)</td>
</tr>
<tr>
<td>Other associations</td>
<td>Autoimmune; Graves’ disease, Hashimoto’s thyroiditis, vitiligo, Addison’s disease, pernicious anemia</td>
</tr>
<tr>
<td>Precipitating and risk factors</td>
<td>Largely unknown; microbial, chemical, dietary, other</td>
</tr>
<tr>
<td>Findings at diagnosis</td>
<td>85%-90% of patients have one and usually more autoantibodies to ICA512/IA-2/IA-2β, GAD65, insulin (IAA)</td>
</tr>
<tr>
<td>Endogenous insulin levels</td>
<td>Low or absent</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Only with hyperglycemia</td>
</tr>
<tr>
<td>Prolonged fast</td>
<td>Mostly present</td>
</tr>
<tr>
<td>Stress, withdrawal of insulin</td>
<td>Hyperglycemia, ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>Euglycemia</td>
</tr>
<tr>
<td></td>
<td>Ketoacidosis</td>
</tr>
<tr>
<td></td>
<td>Nonketotic hyperglycemia, occasionally ketoacidosis</td>
</tr>
</tbody>
</table>

GAD, glutamic acid decarboxylase; IA-2/IA-2β, tyrosine phosphatases; IAA, insulin autoantibodies; ICA, islet cell antibody; ICA512, islet cell autoantigen 512 (fragment of IA-2).

The oral glucose test are between 140 and 200 mg/dL, the pt is also classified as having impaired fasting glucose. Table 3-13 compares type 1 and type 2 DM.

**Diagnosis**

**H&P**
- **PE** varies w/the presence of complications and may be nl in early stages.
- **Diabetic retinopathy:**
  - Nonproliferative (background diabetic retinopathy):
    - Initially: microaneurysms, capillary dilation, waxy or hard exudates, dot and flame hemorrhages, AV shunts
    - Advanced stage: microinfarcts w/cotton wool exudates, macular edema
  - Proliferative retinopathy: characterized by formation of new vessels, vitreal hemorrhages, fibrous scarring, and retinal detachment
- Cataracts and glaucoma occur w↑ frequency in diabetics.
- **Peripheral neuropathy**: pts often complain of paresthesias of extremities (feet more than hands); the sx are symmetric, bilateral, and associated w/intense burning pain (particularly during the night).
  - Mononeuropathies involving cranial nerves (III, IV, and VI), intercostal nerves, and femoral nerves are also common.
• PE may reveal:
  • ↓ Pinprick sensation, sensation to light touch, and pain sensation
  • ↓ Vibration sense
  • Loss of proprioception (leading to ataxia)
  • Motor disturbances (↓ DTRs, weakness and atrophy of interosseous muscles); when the hands are affected, the pt has trouble picking up small objects, dressing, and turning pages in a book.
  • Diplopia, abnormalities of visual fields

■ Autonomic neuropathy:
  • GI disturbances: esophageal motility abnormalities, gastroparesis, diarrhea (usually nocturnal)
  • GU disturbances: neurogenic bladder (hesitancy, weak stream, and dribbling), impotence
  • Orthostatic hypotension: postural syncope, dizziness, lightheadedness
  • Nephropathy: pedal edema, pallor, weakness, uremic appearance
  • Foot ulcers: occur in 15% of diabetics (annual incidence 2%) and are the leading cause of hospitalization. They are usually secondary to PVD, repeated trauma (unrecognized because of sensory loss), and superimposed infections. If a diabetic foot ulcer has been present for weeks and foot pulses are palpable, neuropathy should be considered a major cause.
  • Neuropathic arthropathy (Charcot’s joints): bone or joint deformities from repeated trauma (secondary to peripheral neuropathy)
  • Necrobiosis lipoidica diabeticorum: plaque-like reddened areas w/a central area that fades to white-yellow found on the anterior surfaces of the legs; in these areas, the skin becomes very thin and can ulcerate readily.

Labs
■ Diagnosis is made on the basis of the following tests and should be confirmed by repeated testing on a different day:
  • FBS ≥126 mg/dL (ADA criterion)
  • Nonfasting plasma glucose concentration ≥200 mg/dL
  • Glycohemoglobin (HbA1c): some physicians use this test to make the dx of DM if the random plasma glucose concentration is ≥200 mg/dL and the HbA1c level is >2 standard deviations above the lab mean.
  • Screening for diabetic nephropathy by measuring urine microalb level
  • A fasting serum lipid panel, serum Cr, and electrolytes should be obtained yearly on all adult diabetic pts.

Etiology [see Table 3-13]
Idiopathic Diabetes
■ Type 1 DM
  • Hereditary factors:
  • Islet cell Abs (found in 90% of pts within the first yr of dx)
  • Higher incidence of HLA types DR3, DR4
  • 50% concordance in identical twins
  • Environmental factors: viral infection (possibly coxsackievirus, mumps virus)
■ Type 2 DM
  • Hereditary factors: 90% concordance in identical twins
  • Environmental factor: obesity

Diabetes Secondary to Other Factors
■ Hormonal excess: Cushing’s syndrome, acromegaly, glucagonoma, pheochromocytoma
■ Drugs: glucocorticoids, diuretics, oral contraceptives
■ Pancreatic disease: pancreatitis, pancreatocetomy, hemochromatosis
■ Genetic syndromes: hyperlipidemias, myotonic dystrophy, lipoatrophy
■ Gestational diabetes

Treatment
■ Diet: ↓ fat, ↓ calorie diet
■ Exercise ↑ the cellular glucose uptake by ↑ the number of cell receptors. Consider beginning w/15 min of low-impact aerobic exercise 3×/wk and ↑ the frequency and duration to 30-45 min of moderate aerobic activity 3-5 days/wk.
Chapter 3  Diseases and Disorders

- Weight loss: to ideal BW if the pt is overweight.
- When the preceding measures fail to normalize the serum glucose concentration, oral hypoglycemic agents should be added to the regimen in type 2 DM. Table 3-14 describes commonly used oral hypoglycemic agents.
- Combination Rx of various hypoglycemic agents is commonly used when monotherapy results in inadequate glycemic control.
- Insulin is indicated for the treatment of all pts with type 1 DM and type 2 DM that cannot be adequately controlled w/diet and oral agents. Table 3-15 describes commonly used types of insulin. Replacement insulin Rx should mimic nl release patterns. Approximately 50%-60% of qd insulin should be a basal type consisting of a long-acting insulin (NPH, Ultralente, glargine, detemir) injected once or twice qd; the remaining 40%-50% should be short-acting or rapid-acting to cover mealtime carbohydrates and to correct ↑ current glucose levels.
- In critically ill pts, intensive glucose control ↑ mortality among adults in the ICU in a recent trial (NICE-SUGAR study; N Engl J Med 360:1283, 2009)—a blood glucose target of ≤180 mg/dL resulted in lower mortality than did a target of 81-108 mg/dL.
- Continuous SC insulin infusion (CSII, or insulin pump) provides better glycemic control than conventional Rx and comparable or slightly better control than multiple qd injections. It should be considered for diabetes presenting in childhood or adolescence and during pregnancy.
- Low-dose ASA (ASA; 81 mg/day) to ↓ the risk of cerebrovascular disease
- LDL <70 mg/dL. Use of statins is usually necessary to achieve therapeutic goals.
- BP <125/75. Use of ACEIs for prevention of proteinuria should be considered regardless of BP level.

Clinical Pearl
- Diabetic retinopathy is the most severe of the several ocular complications of diabetes. It occurs in approximately 15% of diabetic pts after 15 yr and ↑ 1%/yr after dx.

133 DIABETIC KETOACIDOSIS (DKA)

Definition
Life-threatening complication of DM caused by severe insulin deficiency manifested clinically by severe dehydration and alterations in the sensorium.

Diagnosis

PE
- Evidence of dehydration (tachycardia, hypotension, dry mucous membranes, sunken eyeballs, poor skin turgor)
- Clouding of mental status
- Tachypnea w/air hunger (Kussmaul’s respiration)
- Fruity breath odor (caused by acetone)
- Lipemia retinalis in some pts
- Possible evidence of precipitating factors (infected wound, pneumonia)
- Abd or CVA tenderness in some pts

Labs
- Glucose level reveals severe hyperglycemia (serum glucose concentration generally >250 mg/dL); urine and serum ketones positive (usually 7-10 mmol/L).
- ABGs reveal acidosis: arterial pH usually <7.30 w/Pco2 >40 mm Hg.
- Serum electrolytes:
  - Serum bicarbonate is usually <18 mEq/L.
  - Serum potassium concentration may be low, nl, or high. There is always significant total body potassium depletion regardless of the initial potassium level.
  - Serum sodium concentration is usually ↓ (pseudohyponatremia) as a result of hyperglycemia, dehydration, and lipemia. Assume 1.6 mEq/L ↓ in extracellular sodium for each 100 mg/dL ↑ in glucose concentration.
  - Calculate the anion gap (AG): AG = Na⁺ – [Cl⁻ + HCO₃⁻]
<table>
<thead>
<tr>
<th></th>
<th>Sulfonylureas</th>
<th>Biguanides</th>
<th>α-Glucosidase Inhibitors</th>
<th>Thiazolidinediones</th>
<th>Meglitinides</th>
<th>Dipeptidyl Peptidase-4 Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic name</strong></td>
<td>Glimepiride, glyburide, glipizide, chlorpropamide, tolbutamide</td>
<td>Metformin</td>
<td>Acarbose, miglitol</td>
<td>Rosiglitazone, pioglitazone</td>
<td>Repaglinide, nateglinide</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>↑↑ Pancreatic insulin secretion chronically</td>
<td>↓↓ HGP; ↓ peripheral IR; ↓ intestinal glucose absorption</td>
<td>Delays PP digestion of carbohydrates and absorption of glucose</td>
<td>↓↓ Peripheral IR; ↑↑ glucose disposal; ↓ HGP</td>
<td>↑↑ Pancreatic insulin secretion acutely</td>
<td>Potentiates insulin synthesis and release</td>
</tr>
<tr>
<td><strong>Preferred patient type</strong></td>
<td>Diagnosis age &gt;30 yr, lean, diabetes &lt;5 yr, insulinopenic</td>
<td>Overweight, IR, fasting hyperglycemia, dyslipidemia</td>
<td>PP hyperglycemia</td>
<td>Overweight, IR, dyslipidemia, renal dysfunction</td>
<td>PP hyperglycemia, insulinopenic</td>
<td></td>
</tr>
<tr>
<td><strong>Therapeutic effects</strong></td>
<td>↓ HBA1c* (%) 1-2 50-70</td>
<td>1-2 50-80</td>
<td>0.5-1 15-30</td>
<td>0.8-1 25-50</td>
<td>1-2 40-80</td>
<td>↓ HBA1c by 0.5%</td>
</tr>
<tr>
<td></td>
<td>↓ FPG* (mg/dL) ~90</td>
<td>80</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Insulin levels</strong></td>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>↑</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Lipids</strong></td>
<td>↓</td>
<td>↓ LDL</td>
<td>↓ TG</td>
<td>↑</td>
<td>↑ Large “fluffy” LDL</td>
<td>—</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Hypoglycemia</td>
<td>Diarrhea, lactic acidosis</td>
<td>Abdominal pain, flatulence, diarrhea</td>
<td>Idiosyncratic hepatotoxicity with troglitazone; edema</td>
<td>Hypoglycemia (low risk)</td>
<td></td>
</tr>
<tr>
<td><strong>Dose(s)/day</strong></td>
<td>1-3 2-3 1-3 1 1-4+ 1</td>
<td>1-3</td>
<td>1</td>
<td>1-4+</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Maximum daily dose (mg)</strong></td>
<td>Depends on agent 2550</td>
<td>150 (&lt;60-kg BW) 300 (&gt;60-kg BW)</td>
<td>Depends on agent 16 (repaglinide) 360 (nateglinide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Range/dose (mg)</strong></td>
<td>Depends on agent 500-1000</td>
<td>25-50 (&lt;60-kg BW) 25-100 (&gt;60-kg BW)</td>
<td>Depends on agent 0.5-4 (repaglinide) 60, 120 (nateglinide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Optimal administration time</strong></td>
<td>–30 min premeal (some with food, others on empty stomach)</td>
<td>With meal</td>
<td>With first bite of meal</td>
<td>Preferably &lt;15 (0-30 min) before meals (omit if no meal)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Main site of metabolism/excretion</strong></td>
<td>Hepatic/renal, fecal</td>
<td>Not metabolized/renal</td>
<td>Only 2% absorbed/fecal</td>
<td>Hepatic/fecal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Values combined from numerous studies; values are also dose dependent.
FPG, fasting plasma glucose; HGP, hepatic glucose production; IR, insulin resistance; PP, postprandial; PPG, postprandial plasma glucose; TG, triglyceride.
Diseases and Disorders

Chapter 3

TABLE 3-15  ■ Types of Insulin

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Brand</th>
<th>Onset (hr)</th>
<th>Peak (hr)</th>
<th>Duration (hr)</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin aspart</td>
<td>NovoLog†</td>
<td>&lt;0.25</td>
<td>1-3</td>
<td>3-5</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin aspart protamine/insulin aspart</td>
<td>NovoLog Mix 70/30†</td>
<td>&lt;0.25</td>
<td>1-4</td>
<td>24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin detemir</td>
<td>Levemir†</td>
<td>1</td>
<td>None</td>
<td>24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Lantus†</td>
<td>1.1</td>
<td>None</td>
<td>≥24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin glulisine</td>
<td>Apidra†</td>
<td>≤0.25</td>
<td>1</td>
<td>2-4</td>
<td>SC, IV</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Humalog†</td>
<td>&lt;0.25</td>
<td>1</td>
<td>3.5-4.5</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin lispro protamine/insulin lispro</td>
<td>Humalog Mix 75/25†</td>
<td>≤0.25</td>
<td>0.5-1.5</td>
<td>24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Humalog Mix 75/25†</td>
<td>≤0.25</td>
<td>0.5</td>
<td>24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin injection regular (R)</td>
<td>Humulin R*</td>
<td>0.5</td>
<td>2-4</td>
<td>6-8</td>
<td>SC, IM, IV</td>
</tr>
<tr>
<td>Insulin regular suspension (NPH)/ regular insulin (R)</td>
<td>Humulin 70/30*</td>
<td>0.5</td>
<td>2-12</td>
<td>24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin suspension (NPH)</td>
<td>Humulin 50/50*</td>
<td>0.5</td>
<td>2-12</td>
<td>24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin suspension (NPH)</td>
<td>Novolin 70/30†</td>
<td>0.5</td>
<td>2-12</td>
<td>24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Humulin N*</td>
<td>1-2</td>
<td>6-12</td>
<td>18-24</td>
<td>SC</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Novolin N†</td>
<td>1.5</td>
<td>4-12</td>
<td>24</td>
<td>SC</td>
</tr>
</tbody>
</table>

*Recombinant (using E. coli).
†Recombinant human insulin analogue (using E. coli).
‡Recombinant (using S. cerevisiae).
§IV to be used in a clinical setting under proper medical supervision.
Injectable insulins listed are available in a concentration of 100 units/mL; Humulin R, in a concentration of 500 unit/mL for SC injection only, is available by prescription from Lilly for insulin-resistant patients who are hospitalized or under close medical supervision.

- In DKA, the AG is ↑ (generally >15); hyperchloremic metabolic acidosis may be present in unusual circumstances when both the GFR and the plasma volume are well maintained.
- CBC w/diff, U/A, urine and blood cultures to r/o infectious precipitating factor.
- Serum Ca, Mg, and phosphorus; the plasma phosphate and Mg levels may be significantly depressed and should be rechecked within 24 hr because they may ↓ further w/correction of DKA.
- BUN and Cr generally reveal significant dehydration.
- Amylase, LFTs should be checked in pts w/abd pain.

 Imaging
- CXR is helpful to r/o infectious process. The initial CXR may be normal if the pt has significant dehydration. Repeat CXR after 24 hr if pulmonary infection is strongly suspected.

 Etiology
- Metabolic decompensation in diabetics usually precipitated by an infectious process (up to 40% of cases). Poor compliance w/insulin Rx and severe medical illness (e.g., CVA, MI) are other common causes. Cocaine abuse has been reported as a risk factor for DKA, particularly in pts w/multiple admissions.

 Treatment
 Fluid Replacement (the usual deficit is 6-8 L)
- Do not delay fluid replacement until laboratory results have been received. Fluid deficits are typically 100 mL/kg of BW.
- The initial fluid replacement should be w/0.9% NS until BP and organ perfusion are restored (usually 1 L or more). In pts w/severe hypernatremia (serum sodium >160 mEq/L), 0.45% saline infusion can be used. Careful monitoring for fluid overload is necessary in elderly pts and those w/h/o CHF.
The rate of fluid replacement varies with the age of the pt and the presence of significant cardiac or renal disease.

The usual rate of infusion is 500 mL–1 L during the first hour; 300-500 mL/hr for the next 12 hr.

Continue the infusion at a rate of 200-300 mL/hr, using 0.45% NS until the serum glucose level is <300 mEq/L, then change the hydrating solution to D5W to prevent hypoglycemia, to replenish free water, and to introduce additional glucose substrate (necessary to suppress lipolysis and ketogenesis).

**Insulin Administration**

- The pt should be given an initial loading IV bolus of 0.15-0.2 U/kg of regular insulin followed by a constant infusion at a rate of 0.1 U/kg/hr (e.g., 25 U of regular insulin in 250 mL of 0.9% saline solution at 70 mL/hr equals 7 U/hr for a 70-kg pt). Insulin replacement should generally not be started until serum potassium level is >3.3 mEq/L to prevent life-threatening hypokalemia.
- Monitor serum glucose qh for the first 2 hr, then monitor q2-4h.
- The goal is to ↓ serum glucose level by 80 mg/dl/hr (after an initial drop because of rehydration); if the serum glucose level is not ↓ at the expected rate, double the rate of insulin infusion.
- When the serum glucose level approaches 250 mg/dL, ↓ the rate of insulin infusion to 2-3 U/hr and continue this rate until the pt has received adequate fluid replacement, HCO3⁻ is close to nl, and ketones have cleared.
- Approximately 30-60 min before the IV insulin infusion is stopped, administer an SC dose of regular insulin (dose varies w/the pt’s demonstrated insulin sensitivity); this SC dose of regular insulin is necessary because of the extremely short life of the insulin in the IV infusion.
- When the pt is able to eat, NPH insulin 10-15 U is given in the morning and regular insulin is administered before each meal and at hs by use of a sliding scale. In newly diagnosed diabetics, the total qd dose to maintain metabolic control ranges from 0.5-0.8 U/kg/day. Split-dose Rx w/regular and NPH insulin may be given, w/½ of the total qd dose administered in the morning and ½ in the evening.

**Electrolyte Replacement**

**Potassium replacement:** The average total potassium loss in DKA is 300-500 mEq.

- The rate of replacement varies with the pt’s serum potassium level, degree of acidosis (↓ pH, ↑ potassium level), and renal function (potassium replacement should be used w/caution in pts w/renal failure).
- As a rule of thumb, potassium replacement may be started when serum K⁺ < 5.2 mEq/L or there is no ECG evidence of hyperkalemia (tall, narrow, or tent-shaped T waves, ↓ or absent P waves, short QT intervals, widening of QRS complex).
- In pts w/nl renal function, potassium replacement can be started by adding 20-40 mEq KCl/L of IV hydrating solution if serum potassium level is 4-5 mEq/L, more if serum potassium level is lower than 4 mEq/L. In pts w/severe hypokalemia (potassium <3.3 mEq/L) hold insulin therapy and give 40 mEq of potassium/hr until potassium is >3.3 mEq/L.
- Monitor serum potassium level qh for the first 2 hr, then monitor q2-4h.

**Phosphate replacement:** If the serum PO4 is <1.0 mg/dL give 20 to 50 mmol/L of potassium phosphate. Routine replacement of phosphate (in absence of laboratory evidence of significant hypophosphatemia) is not indicated. Rapid IV phosphate administration can cause hypocalcemia.

**Mg replacement:** Replacement is indicated only in the presence of significant hypomagnesemia or refractory hypokalemia.

**Bicarbonate Rx**

- Routine use of bicarbonate in DKA is contraindicated because it can worsen hypokalemia and intracellular acidosis and cause cerebral edema. Bicarbonate Rx should be considered only if the arterial pH is <6.9 and HCO3⁻ is <5. In these pts, 44-88 mEq of sodium bicarbonate can be added to a liter of 0.45% NS q2-4h until pH ↑ >7. Use of bicarbonate Rx is particularly dangerous in the pediatric population. Children w/DKA who...
have low partial pressures of arterial CO₂ and high serum urea nitrogen concentration at presentation and who are treated w/bicarbonate are at ↑ risk for cerebral edema. Bicarbonate Rx in children w/DKA should be limited to those w/severe circulatory failure and a high risk of cardiac decompensation resulting from profound acidosis.

Clinical Pearls
- Although DKA occurs more commonly in type 1 DM, a significant proportion (>20%) occurs in pts w/type 2 DM.
- 20% of DKA admissions involve newly diagnosed diabetes.

134 DIARRHEA

Definition
Frequent passage of loose or watery stools amounting to >200 g in 24 hr. A more useful definition is an ↑ in the frequency of stools w/↓ in consistency compared w/the pt’s baseline. Traveler’s diarrhea is the passage of at least 3 unformed stools in a 24-hr period, accompanied by N/V and abd cramps occurring during or within 10 days of travel to another country. Chronic diarrhea is the passage of >200 g of stool/day for >3 wk.

Diagnosis

Hx
- Travel hx (traveler’s diarrhea)
  - Recent travel to areas or countries w/poor sanitation: toxigenic and invasive Escherichia coli, parasites (Giardia, Entamoeba histolytica, rotavirus, Norwalk virus)
  - Outdoor living in wilderness areas w/ingestion of water from streams: Giardia (particularly in Rocky Mountain region, northern New England). Giardia is the most common water-borne parasite that causes diarrhea.
  - Yersinia enterocolitica is found predominantly in cooler geographic areas (e.g., Canada).
  - Ingestion of raw shellfish from Gulf of Mexico or Mexico: Plesiomonas shigelloides
  - Ingestion of untreated fresh water: Aeromonas hydrophila (particularly in Thailand)
  - Travel to Russia: Cryptosporidium, Giardia
  - Seasonal variation
    - Rainy summer season: enterotoxigenic E. coli, Shigella, Salmonella
    - Dry winter season: C. jejuni
- Temporal characteristics
  - Duration of diarrhea: diarrhea of short duration (1-3 days) associated w/mild sx usually has a viral cause (rotavirus, Norwalk agent); diarrhea lasting longer than 3 wk probably is not bacterial or viral.
  - Time of day: nocturnal diarrhea is common w/diabetic neuropathy.
  - Relationship to meals
    - Onset within minutes: scambroid poisoning (N/V, flushing, diarrhea)
    - Onset within hours after a particular meal: toxins (Staphylococcus aureus, toxigenic E. coli, Clostridium perfringens, Bacillus cereus, Vibrio parahaemolyticus, ciguatera toxin [paresthesia, weakness])
    - Diarrhea secondary to Salmonella, Shigella, Campylobacter, and Yersinia has a longer incubation period.
  - Related to stress: “functional” diarrhea, IBS
  - Diarrhea alternating w/constipation: IBS
- Diet
  - Ingestion of foods containing sorbitol or mannitol may cause osmotic diarrhea.
  - Diarrhea after ingestion of dairy food products may be caused by lactose intolerance.
  - Shellfish ingestion: Norwalk agent, Vibrio cholerae, V. mimicus, V. parahaemolyticus, P. shigelloides
  - Chinese food (fried rice): B. cereus
  - Undercooked hamburger: E. coli serotype O157:H7
  - Milk: B. cereus, Campylobacter spp, Listeria, C. perfringens, Salmonella
  - Poultry, eggs: Campylobacter spp, Salmonella, S. aureus
- Salads: Norwalk virus, *Salmonella, Shigella*
- Raspberries: *Cyclospora*
- Mahi-mahi, mackerel, tuna: scambroid
- Barracuda, grouper, red snapper: ciguatera toxin

### Activities
- Long-distance runners may experience bloody diarrhea secondary to bowel ischemia.
- Institutionalized pts have a higher incidence of bacterial and parasitic infections.
- Daycare centers: rotavirus, *Giardia, Salmonella, Shigella, Cryptosporidium, Campylobacter*

### Medications
- Almost any drug can cause diarrhea; following is a list of commonly used medications:
  - Mg-containing antacids, misoprostol, PPIs
  - Methylxanthines (caffeine, theophylline)
  - Laxatives
  - Lactulose
  - Colchicine
  - Quinidine, digitalis, propranolol, and other antiarrhythmic agents
  - Nutritional supplements
  - Metformin
  - Artificial sweeteners (sorbitol, mannitol)
  - Thyroxine
  - Abx
- Abx-induced pseudomembranous colitis should be suspected in any pt receiving abx: a positive test result for *C. difficile* toxin w/the stool assay, cytotoxin test, or commercially available immunoassays confirms the dx. Diarrhea may be noted to be far removed from the time of abx ingestion.

### Sexual habits
- Male homosexuals have a higher incidence of bacterial and parasitic intestinal infections (e.g., *Giardia lamblia, E. histolytica, Cryptosporidium, Salmonella, N. gonorrhoeae, Campylobacter*).

### Relevant medical hx
- Surgical hx (ileal resection, gastrectomy, cholecystectomy)
- Abd irradiation
- DM
- Hyperthyroidism
- Watery diarrhea in an elderly pt w/chronic constipation may be caused by fecal impaction or obstructing carcinoma.
- AIDS: *Cryptosporidium, Salmonella, CMV, Mycobacterium avium-intracellulare, Kaposi’s sarcoma involving the gut, AIDS enteropathy, Cyclospora* spp (cyanobacterium-like bodies)
- H/o laxative abuse (pt may deny)
- Proteinuria, neuropathy: amyloidosis, DM
- Organ transplantation, cancer chemotherapy, steroid Rx, AIDS: CMV

### Associated sx
- Tenderness, fever, weight loss (IBD, amebiasis, lymphoma, tuberculosis)
- Abd pain and significant weight loss (carcinoma of pancreas or other malignant neoplasms)
- Weight loss despite good appetite (malabsorption, hyperthyroidism)
- Diarrhea and PUD (Zollinger-Ellison syndrome, gastrinoma, gastrocolic fistula)
- Flushing and bronchospasm (carcinoid syndrome)
- LLQ pain, fever, w/ or w/o bloody diarrhea (diverticulitis)
- Arthritis (IBD, Whipple’s disease)
- Bloody diarrhea, hemolytic-uremic syndrome, thrombocytopenic purpura (*E. coli* O157:H7)

### Characteristics of the stool (from pt’s hx)
- Large, foul smelling (malabsorption)
- ↑ Mucus (IBS)
- Watery stools (psychosomal disturbances, fecal impaction, colon carcinoma, IBD or IBS, *Cyclospora* infection, pancreatic cholera [vasoactive intestinal peptide]).
**PE**

May include signs of dehydration, in general. Signs and sx of specific disorders are described:
- Rectal fistulas, RLQ abd mass (Crohn’s disease)
- Arthritis, iritis, uveitis, erythema nodosum (IBD)
- Abd masses (neoplasms of colon, pancreas, or liver; diverticular abscess [LLQ mass], IBD)
- Flushing, bronchospasm (carcinoid syndrome)
- Buccal pigmentation (Peutz-Jeghers syndrome)
- ↑ Pigmentation (Addison’s disease)
- Ammoniac or urinary breath odor (renal failure)
- Ecchymosis (vitamin K deficiency secondary to malabsorption of fat-soluble vitamins, celiac disease)
- Fever (IBD, infectious diarrhea, lymphoma)
- Goiter, tremor, tachycardia (hyperthyroidism)
- Lymphadenopathy (neoplasm, lymphoma, tuberculosis, AIDS, Whipple’s disease)
- Macroglossia (amyloidosis)
- Kaposi’s sarcoma (AIDS)

**Initial Evaluation**

- Labs (may not be necessary in pts who do not appear significantly ill or dehydrated)
  - CBC: ↑↑ WBCs w/shift to left may indicate infectious process; ↓ Hb/Hct levels may indicate anemia from blood loss; ↑ Hct may indicate dehydration.
  - Serum lytes: hypokalemic from diarrhea, hypernatremia from dehydration, or less commonly hyponatremia from ADH compensation
  - BUN, Cr may be ↑ from dehydration.
  - ELISA stool antigen test for giardia (when suspected).
- Stool sample: most cases of diarrhea are self-limited, and stool evaluation is generally not necessary. Stool cultures should be considered only if the pt has fever and bloody diarrhea or is immunocompromised. If a stool sample has been obtained, the following tests should be considered:
  - Occult blood (positive in IBD, bowel ischemia, some bacterial infections)
  - Löffler’s alkaline methylene blue stain for fecal leukocytes (positive result in inflammatory diarrhea caused by *Salmonella, Campylobacter, Yersinia, Shigella*, invasive *E. coli*, although the sensitivity of this test is relatively low).
  - Bacterial cultures only in selected pts w/presence of blood in the stool and suspected infectious diarrhea (*Salmonella, Shigella, Campylobacter, Yersinia, E. coli* O157:H7); cultures for *N. gonorrhoeae* should be considered in active male homosexual pts.
  - Examination for O&P; indirect hemagglutination test for *E. histolytica* is useful when amebiasis is suspected and stool examination findings are inconclusive.
  - *C. difficile* toxin to r/o pseudomembranous colitis in pts receiving abx
  - Modified Ziehl-Neelsen stain, acid fast, or auramine stain in immunocompromised pts w/suspected *Cryptosporidium* infection
- Abd x-rays (flat plate and upright) are indicated only in pts w/abd pain or evidence of obstruction to r/o toxic megacolon and bowel ischemia; pancreatic calcifications are suggestive of pancreatic insufficiency.

**Initial Treatment**

- NPO: fasting usually results in cessation of osmotic diarrhea.
- IV hydration in hospitalized pts
- Correct electrolyte abnormalities.
- Discontinue possible causative agents (e.g., antacids containing Mg, abx).
- Antiperistaltic agents (e.g., diphenoxylate) should be used w/caution in pts suspected of having IBD or infectious diarrhea; loperamide or bismuth subsalicylate may be helpful in cases of mild diarrhea.
- If diarrhea persists and a bacterial or parasitic organism is identified, abx Rx should be started.
Diseases

Diarrhea

Etiology

- Colonic
- Endocrine
- Postsurgical
- Functional
- Parasitic
- Malabsorptive
- IBD
- IBS

Diarrhea

Traveler’s diarrhea

- It is most commonly caused by enterotoxigenic E. coli.
- Diarrhea that does not respond to oral loperamide within a few hours can be treated w/ a 3-day course of rifamixin 200 mg tid) or quinolones (e.g., ciprofloxacin [500 mg bid]). Some authorities endorse a single 750-mg dose of ciprofloxacin for mild cases.
- Azithromycin (500 mg/day for 3 days) is also effective against most cases of traveler’s diarrhea, including those that are quinolone resistant.

Diarrhea caused by Salmonella in pts w/HIV infection can be treated w/ amoxicillin 1 g tid for 3-14 days, ciprofloxacin 500 mg bid for 7 days, or trimethoprim or sulframethoxazole bid for 14 days.

Diarrhea in pts w/ IBS is treated w/ psyllium or other fiber products and by decreasing caffeine, chocolate, alcohol intake, and stress. Antispasmodics (dicyclomine, hyoscyamine) can be added in resistant cases.

Evaluation of Patient w/ Chronic or Recurrent Diarrhea

Etiology

- Drug induced (including laxative abuse)
- IBS
- Lactose intolerance
- IBD
- Malabsorptive diseases (e.g., mucosal disease, pancreatic insufficiency, bacterial overgrowth)
- Parasitic infections (giardiasis, amebiasis)
- Functional diarrhea
- Postsurgical (partial gastrectomy, ileal resection, cholecystectomy)
- Endocrine disturbances
  - DM (↓ sympathetic input to the gut)
  - Hyperthyroidism
  - Addison’s disease
- Gastrinoma (Zollinger-Ellison syndrome)
- VIPoma (pancreatic cholera)
- Carcinoid tumors (serotonin)
- Medullary carcinoma of thyroid (calcitonin)
- Pelvic irradiation
- Colonic carcinoma (e.g., villous adenoma)
- Collagenous colitis: typical patient is middle-aged woman, nl endoscopy findings, subepithelial acellular collagen band on bx of the sigmoid or right colon; sx resolution w/ sulfasalazine alone or combined w/ steroids
Lymphocytic colitis: similar to collagenous colitis except that lymphocytic infiltration is present and there is no collagen band. Treatment is the same. The prevalence is the same in both sexes.

**Diagnosis**
- H&P and initial labs are the same as for new-onset diarrhea.
- Additional laboratory evaluation:
  - Sudan III stain of stool for presence of fat droplets and meat fibers; their presence indicates malabsorption.
  - If the CBC shows macrocytic indices, obtain vitamin B₁₂ and red blood cell folate levels to rule out megaloblastic anemia secondary to malabsorption.
  - Mg-induced diarrhea can be diagnosed w/ a quantitative fecal analysis for soluble Mg.
  - 24-hr urine collection for 5-HIAA in pts w/suspected carcinoid syndrome; serum gastrin level in pts w/suspected Zollinger-Ellison syndrome.
  - Measure the stool osmolality to evaluate for factitial diarrhea. The presence of hypotonic stools may indicate Munchausen syndrome or malingering. Because the colon does not excrete free water, fecal hypotonicity indicates the addition of water, urine, or another hypotonic fluid.
- Secretory diarrhea results from impaired absorption or excessive intestinal secretion of electrolytes (fecal fluid contains large amounts of electrolytes); following is a list of common causes of secretory diarrhea:
  - Enteric infections
  - Neoplasms of exocrine pancreas (vasoactive intestinal peptide, gastric inhibitory polypeptide, secretin, glucagon)
  - Bile salt enteropathy
  - Villous adenoma
  - IBD
  - Carcinoid tumor
  - Celiac sprue
  - Ingestion of cathartic agents
- Osmotic diarrhea results from impaired water absorption secondary to osmotic effect of nonabsorbable intraluminal molecules; following is a list of common causes of osmotic diarrhea:
  - Lactose and other disaccharide excess, pancreatic insufficiency
  - Drug induced (lactulose, sorbitol, sodium sulfate, antacids)
  - Postsurgical (gastrojejunoanostomy, vagotomy and pyloroplasty, intestinal resection)
- The dx of osmotic diarrhea can be made by showing an “osmotic gap” in stool analysis.
  \[
  \text{Osmotic gap} = \text{Measured osmolality} - 2(\text{[Na}^+] + \text{[K}^+])
  \]
  A difference between calculated and actual osmolality > 50 is consistent w/osmotic diarrhea.

**DIFFUSE INTERSTITIAL LUNG DISEASE**

**Definition**
Large group of nonmalignant disorders characterized by diffuse damage to the lung parenchyma through inflammation and fibrosis or granulomatous reaction in interstitial or vascular areas.

**Diagnosis**
- **H&P**
  - Progressive dyspnea and nonproductive cough; other clinical manifestations vary w/ the underlying disease process.
  - PE typically shows end-respiratory dry rales (*Velcro rales*), cyanosis, clubbing, and right-sided heart failure.

**Imaging**
- CXR may be nl but commonly shows a bibasilar reticular pattern.
- High-resolution CT: superior to CXR; also useful for determining potential bx sights.
**DIGITALIS TOXICITY**

**Labs**
- ABGs may be nl or show respiratory alkalosis.
- ANA, ANCA, RF, LDH
- PFTs: consistent w/restrictive disease (↓ VC, ↓ TLC, ↓ RV and ↓ diffusing capacity)
- Bronchoscopy w/bronchioloalveolar lavage: in selected pts
- Open lung bx or transbronchial bx

**Etiology**
- Occupational and environmental exposure: pneumoconiosis, asbestosis, organic dust, gases, fumes, berylliosis, silicosis
- Granulomatous lung disease: sarcoidosis, infections (e.g., fungal, mycobacterial)
- Drug induced: bleomycin, busulfan, MTX, chlorambucil, cyclophosphamide, BCNU (carmustine), gold salts, tetrazolium chloride, amiodarone, tocainide, PCN, zidovudine, sulfonamide
- Radiation pneumonitis
- Connective tissue diseases: SLE, RA, dermatomyositis
- IPF: bronchiolitis obliterans, interstitial pneumonitis, desquamative interstitial pneumonitis
- Infections: viral pneumonia, Pneumocystis pneumonia
- Others: Wegener’s granulomatosis, Goodpasture’s syndrome, eosinophilic granuloma, lymphangitic carcinomatosis, chronic uremia, chronic gastric aspiration, hypersensitivity pneumonitis, lipid pneumonia, lymphoma, lymphoid granulomatosis

**Treatment**
- Supplemental O₂ in pts w/hypoxemia
- Prednisone 0.5-1 mg/kg qd × 4-12 wk. Pts should be re-evaluated after this initial course of treatment. If they are stable, steroids may be tapered. If not, the same course may be maintained for another 4-12 wk. If condition continues to decline, addition of second agent (cyclophosphamide, azathioprine) may be considered.

**Clinical Pearl**
- Consider lung transplantation in selected pts w/intractable end-stage ILD.

**DIGITALIS TOXICITY**

**Diagnosis**

**H&P**
- Cardiac: most common and often first finding is ↑ PVCs; can present w/almost any dysrhythmia or conduction block
- GI: anorexia, N/V, diarrhea, abd pain
- CNS: headache, dizziness, visual disturbance (flashing lights, halos, blurred vision, change in color perception (blue/green), ↓ visual acuity), confusion, hallucinations, delirium

**Labs**
- Stat digoxin level (in acute ingestion, high levels may not be toxic as tissue redistribution will occur)
- Serum lytes, BUN, Cr, Mg, Ca
- Hyperkalemia often seen in acute poisoning; hypokalemia more common in chronic toxicity

**ECG**
- Almost any dysrhythmia can occur, but simultaneous ↑ automaticity of cardiac tissue and conduction delay in the AV node should raise suspicion. Findings suggestive of toxicity include the following:
  - Frequent PVCs
  - Bradydysrhythmias
  - AV block (Mobitz type I)
  - Atrial tachycardia w/AV block
  - Junctional tachycardia
  - Bidirectional VT (Fig. 3-19)
  - PAT is most specific for digoxin toxicity
Diseases

Chapter 3  Diseases and Disorders

Acquired diseases

Definition

FIGURE 3-19. This digoxin toxic arrhythmia is a special type of ventricular tachycardia (bidirectional tachycardia) with QRS complexes that alternate in direction from beat to beat. No P waves are present.

Treatment

- Acute toxicity: activated charcoal if within 1 hr of ingestion
- Treat hyperkalemia, hypokalemia, and/or hypomagnesemia.
- Digoxin-specific Fab fragments (Digibind):
  - Specific Abs that bind to digoxin and to a lesser extent other cardiac glycosides
  - Initial response is usually seen in 30 min, and complete reversal usually occurs within 4 hr.
  - Indications: hyperkalemia (≥5 mEq/L), severe arrhythmias, massive OD (acute ingestion of ≥10 mg digoxin or digoxin serum level ≥10 ng/mL), co-ingestion of cardiotoxic drugs or plants containing cardiac glycosides
  - Dosing: 1 vial (38 mg) of Fab fragments binds 0.5 mg of digoxin.
  - Acute ingestion: number of vials = [ingested digoxin mg × 0.8]/0.5
  - Chronic ingestion: number of vials = [(serum digoxin level ng/ml) × weight kg]/100
  - If neither the amount ingested nor serum level is known, treat empirically.
    - Acute intoxication—10 vials and repeat if needed
    - Chronic toxicity—6 vials
  - NOTE: Underdosing of Fab fragments may result in rebound toxicity as free digoxin is released from tissue stores.
  - After use of Fab fragments, the free digoxin level ↓, but the measured digoxin level may ↑ because most assays measure free and bound digoxin levels. Serum levels are unreliable for days.
  - Inactive complexes are excreted in urine; half-life of complex is 15-20 hr. In renal failure, consider plasma exchange or plasmapheresis to remove Fab-digoxin complex; theoretically, complexes may dissociate before excretion and toxicity may recur.

- Adverse effects of treatment:
  - May undo desirable action of drug and exacerbate heart failure or ↑ ventricular response in previously controlled AF
  - Hypokalemia: monitor potassium level hourly for several hours. The hyperkalemia seen in toxicity reflects a change in potassium distribution, not an ↑ in total body stores. As toxicity resolves, the potassium moves back into the cell and hypokalemia can occur.
  - Allergic reactions (<1%)
  - Hemodialysis and hemoperfusion: not useful because of extensive tissue binding and large volume of distribution

Clinical Pearls

- Falsely ↑ digoxin levels may be seen in pregnant women, renal failure, hepatobiliary disease, and CHF because of the presence of an endogenous digoxin-like substance.
- Severe toxicity from ingestion of nondigoxin cardiac glycosides (e.g., plants) may present w/only mildly ↑ digoxin levels because of low cross-reactivity between these substances and the digoxin assay.

DIC

Definition

Acquired thromboembolic disorder characterized by generalized activation of the clotting mechanism, which results in microangiopathic hemolysis and the
intravascular formation of fibrin and ultimately thrombotic occlusion of small and midsize vessels.

**Diagnosis**
- Peripheral blood smear generally shows RBC fragments (schistocytes) and ↓ platelet count.
- Coagulation factors are consumed at a rate in excess of the capacity of the liver to synthesize them, and platelets are consumed in excess of the capacity of the bone marrow megakaryocytes to release them. Diagnostic characteristics of DIC are ↑ PT, PTT, TT, fibrin split products, D-dimer; ↓ fibrinogen level, thrombocytopenia.
- Coagulopathy secondary to DIC must be differentiated from that secondary to liver disease or vitamin K deficiency.
- Vitamin K deficiency is manifested w/↑ PT and nl PTT, TT, platelet count, and fibrinogen level; PTT may be ↑ in severe cases.
- Pts w/liver disease have abnl PT and PTT; TT and fibrinogen are usually nl unless severe disease is present; platelets are usually nl unless splenomegaly is present.
- Factors V and VIII are ↓ in DIC, but they are nl in liver disease w/ coagulopathy.

**Etiology**
- Infections (e.g., gram-negative sepsis, RMSF, malaria, viral or fungal infection)
- Obstetric complications (e.g., dead fetus, amniotic fluid embolism, toxemia, abruptio placentae, septic abortion, eclampsia)
- Tissue trauma (e.g., burns, hypothermia-rewarming)
- Neoplasms [e.g., adenocarcinomas [GI, prostate, lung, breast], acute promyelocytic leukemia]
- Quinine, cocaine-induced rhabdo
- Liver failure
- Acute pancreatitis
- Transfusion reactions
- Respiratory distress syndrome
- Other: SLE, vasculitis, aneurysms, polyarteritis, cavernous hemangiomas

**Treatment**
- Correct and eliminate underlying cause (e.g., antimicrobial Rx for infection).
- Replacement Rx w/FFP and platelets in pts w/significant hemorrhage:
  - FFP 10-15 mL/kg can be given w/goal of normalizing INR.
  - Platelet transfusions are given when platelet count is <10,000 (or higher if major bleeding is present).
- Cryoprecipitate 1 U/5 kg is reserved for hypofibrinogen states.
- Antithrombin III treatment may be considered as a supportive therapeutic option in pts w/severe DIC. Its modest results and substantial cost are limiting factors.
- Heparin Rx at a dose lower than that used in venous thrombosis (300-500 U/hr) may be useful in selected cases to ↑ neutralization of thrombin (e.g., DIC associated w/acute promyelocytic leukemia, purpura fulminans, acral ischemia).

**Clinical Pearl**
- The treatment of chronic DIC is controversial. Low-dose SC heparin and combination antiplatelet agents such as ASA and dipyridamole may be useful.

### DIVERTICULAR DISEASE

**Definitions**
- **Colonic diverticula**: herniations of mucosa and submucosa through the muscularis generally found along the colon’s mesenteric border at the site where the vasa recta penetrates the muscle wall (anatomic weak point).
- **Diverticulosis**: asymptomatic presence of multiple colonic diverticula.
- **Diverticulitis**: inflammatory process or localized perforation of diverticulum.
Diagnosis

H&P
- PE in pts w/diverticulosis is generally nl.
- Painful diverticular disease can present w/LLQ pain, often relieved by defecation; location of pain may be anywhere in the lower abd because of the redundancy of the sigmoid colon.
- Diverticulitis can cause muscle spasm, guarding, and rebound tenderness predominantly affecting the LLQ.
- Diverticular bleed: bleeding is painless and stops spontaneously in the majority of pts (60%); it is usually caused by erosion of a blood vessel by a fecalith present within the diverticular sac.

Labs
- ↑ WBC w/left shift: diverticulitis
- Microcytic anemia: in pts w/chronic bleeding from diverticular disease. MCV may be elevated in acute bleeding secondary to reticulocytosis.

Imaging
- CT of abd: sensitivity of 93%-97% and a specificity approaching 100% for diverticulosis. Typical findings are thickening of the bowel wall, fistulas, and abscess formation. CT may also reveal other disease processes (e.g., appendicitis, tubo-ovarian abscess, Crohn’s disease) accounting for lower abd pain.
- If diverticular bleeding is suspected:
  - Arteriography if the bleeding >1 mL/min
  - Technetium Tc 99m sulfa colloid
  - Technetium Tc 99m–labeled RBC (can detect bleeding rates as low as 0.12-5 mL/min)

Treatment

Diverticulosis
- ↑ Dietary fiber intake and regular exercise

Diverticulitis
- Mild case: broad-spectrum PO abx (e.g., ciprofloxacin 500 mg bid to cover aerobic component of colonic flora and metronidazole 500 mg q6h for anaerobes) and liquid diet for 7-10 days
- Severe case: NPO and aggressive IV abx Rx
  - Ampicillin-sulbactam 3 g IV q6h or
  - Piperacillin-tazobactam 4.5 g IV q8h or
  - Ciprofloxacin 400 mg IV q12h + metronidazole 500 mg IV q6h or
  - Cefoxitin 2 g IV q8h plus metronidazole 500 mg IV q6h
- Life-threatening case: imipenem 500 mg IV q6h or meropenem 1 g IV q8h
- Surgical treatment: resection of involved area, diverting colostomy w/ reanastomosis performed when infection has been controlled

Diverticular Hemorrhage
- Blood replacement and correction of volume and any clotting abnormalities
- Colonoscopic treatment w/epinephrine injections, bipolar coagulation, or both may prevent recurrent bleeding and ↓ the need for surgery.
- Surgical resection if bleeding does not stop spontaneously after administration of 4-5 U of PRBCs or recurs w/severity within a few days; if attempts at localization are unsuccessful → total abd colectomy w/ileoproctostomy.

Clinical Pearl
- 70% of diverticular bleeding occurs in the right colon.

139 DUMPING SYNDROME

Definition
Constellation of postprandial sx as a result of rapid delivery of stomach contents into the small bowel after surgery for PUD. The rapid release of hypertonic chyme into the duodenum causes intravascular volume depletion given the osmotic gradient it creates. Subsequent peak in blood sugar is followed by rapid release of insulin, which results in a hypoglycemic state.
Diagnosis
- The majority of pts usually present w/early dumping sx or combination of early and late sx.
- Early dumping: sx start <1 hr after eating food; N/V and belching, epigastric fullness, cramping, and diarrhea
- Late dumping: sx occur >1-3 hr after eating; diaphoresis, irritability, difficulty concentrating
- Typically the dx is made on clinical grounds. In certain clinical settings (e.g., sx in pts w/no prior h/o gastric surgery), additional evaluation, including oral glucose challenge and imaging studies, may be pursued.

Etiology
- Dumping syndrome occurs almost exclusively in pts having gastric surgery.
- Systemic sx are thought to be due to hypovolemia caused by rapid shifts of fluid from the intravascular space into the lumen of the bowel.
- ↑ in vasoactive substances is thought to play a role in dumping syndrome.
- Late dumping sx are thought to be due to reactive hypoglycemia.

Treatment
- Diet modification
  - Divide calorie intake in six small meals.
  - ↓ Fluid intake w/meals (try to avoid 30 min before meals).
  - ↓ Carbohydrate intake and avoid simple sugars.
  - ↑ Supplement dietary fibers.
  - Avoid milk/milk products.
- Acarbose 50 mg PO qd if dietary modification does not help.
- Octreotide 25-50 µg SC 30 min before meals is effective in relieving sx of dumping syndrome.
- Surgery in pts w/severe sx refractory to dietary and acute general treatment. Procedures include reconstruction of the pylorus, conversion of a Billroth II to a Billroth I anastomosis, and a Roux-en-Y reconstruction.

140 ECHINOCOCCOSIS

Definition
Chronic infection caused by the larval stage of several animal cestodes (flat worms) of the genus Echinococcus. E. granulosus is the cause of cystic hydatid disease, E. multilocularis and E. vogeli are the causes of alveolar and polycystic disease.

Diagnosis
Labs
- Ab assays (ELISA and Western blot): >90% sensitive and specific for liver cysts but less accurate for cysts in other sites
- Histologic examination of cyst or contents obtained by aspiration or resection (if possible) will confirm dx.

Imaging
- U/S and CT scan: both are sensitive for the detection of cysts, especially in the liver; however, both lack specificity and are inadequate to establish the dx of echinococcosis w/certainty.

Treatment
- Echinococcal cysts: surgical resection. If resection is not feasible, perform percutaneous drainage w/instillation of 95% ethanol to prevent dissemination of viable larvae. Surgical Rx is followed by medical Rx w/albendazole.
- Echinococcosis confined to the liver:
  - Albendazole (400 mg bid for 28 days followed by 14 days of rest for at least 3 cycles)
  - Mebendazole (50-70 mg/kg qd) if albendazole is not available

Clinical Pearl
- Long-term follow-up necessary after surgical or medical Rx because of ↑ incidence of late relapse. Ab assays and imaging studies should be repeated q6-12mo for several years after successful surgical or medical Rx.
141 EHRlichiosis (Human Granulocytic EHRlichiosis; HGE ANAPlasmosis)

**Definition**
Zoonotic infection of granulocytes, caused by an *Ehrlichia* species closely related to *E. phagocytophila*, *E. equi*, and *E. ewingii*, w/multisystem manifestations. The etiologic agent is now known as *Anaplasma phagocytophilum*.

**Diagnosis**
**H&P**
- Most common initial sx: fever, chills, rigor, headache, myalgia
- Subsequent sx: anorexia, nausea, arthralgia, cough, delirium, abd pain, rash (<11%)  
- Complications: hepatitis, interstitial pneumonitis, renal and respiratory failure, meningitis

**Labs**
- Giemsa-stained smear demonstrating morulae of the organism within granulocytes
- CBC: progressive leukopenia and thrombocytopenia w/nadir near day 7
- LFTs: ALT, AST, LDH, alk phos
- Serologic titer (IFA) >80 or 4-fold ↑ in titer to *E. equi* antigen
- + PCR
- Culture on the first 7 days of illness; not readily available in most clinical laboratories

**Imaging**
- CXR: interstitial pneumonitis (unusual)
- MRI of the brain

**Etiology**
- Obligate intracellular gram-negative bacterium (family Rickettsiaceae, genus *Ehrlichia*), now renamed *Anaplasma phagocytophilum*
- Vector
  - Almost certainly tick borne, recently confirmed to be rarely transmitted by infected blood
  - Transmitted by *Ixodes scapularis* in the northeastern and upper midwestern states and *Ixodes pacificus* in the Pacific western states
  - Tick exposure reported in >90% of pts, w/approximately 60% reporting tick bite
- Mammalian host: deer, horses, dogs, white-footed mice, cattle, sheep, goats, bison
- Host inflammatory and immune responses define final spectrum of disease beyond granulocytes, including hepatitis, interstitial pneumonitis, and nephritis w/mild azotemia.
- 6%-21% of pts w/HGE also have serologic evidence of other *Ixodes* spp tick-borne diseases: Lyme disease or babesiosis.

**Treatment**
- Doxycycline: 100 mg bid × 10-14 days for adults
- Rifampin: 300 mg bid × 7-10 days can be used in pregnancy.
- Recovery is usual outcome; fatality rate of HGE is <1%.

**Clinical Pearl**
- Duration of time tick must be attached to produce illness is usually ≥24 hr.

142 ELECTRICAL INJURY

**Definition**
Injuries or wounds that occur as a result of contact w/an electrical current.

**Diagnosis**
**H&P**
- Cognitive changes: depending on the extent of injury, the pt may be unconscious, seizing, or confused and unable to present hx.
- Extensive burns (>10% of the body surface)
  - Located over the entry and exit sites
  - Most common entry sites are the hands and skull.
  - Most common exit sites are the heels.
• **Kissing burns** over the flexor creases
• Usually on the superficial partial thickness of the skin
• Oral burns are common in children; bleeding from the labial artery may present 7-10 days after the injury.

- Fxs
- Compartment syndrome from severe muscle tissue damage, renal failure
- Headaches
- Weakness and paresthesias
- Motor and sensory deficits
- Otologic injury, conductive loss secondary to tympanic membrane rupture or ossicular disruption
- Pneumothorax
- Stricture of the esophagus (delayed presentation)

**Labs**
- CBC, lytes, BUN/Cr, ABGs, myoglobin, CK
- U/A: myoglobinuria
- LFTs
- Type and crossmatch

**Imaging**
- ECG: asystole or VF may be the initial presenting rhythm
- X-ray: any suspicious area for bone Fxs
- CT scan of the head and skull: in pts w/major head injury

**Etiology**
- Electricity causes tissue injury by converting electrical energy into heat or by blunt trauma from being thrown from the electrical source or from continuous muscle contraction (tetany).
- The effects of electricity are determined by 7 factors: type of current, amount of current, pathway of current, duration, area of contact, resistance of the body, and voltage.
- Tissue damage is > w/higher voltage and longer duration of contact.
- Direct current (DC) contact causes a single muscle contraction, throwing the pt away from the source. Alternating current (AC) contact precipitates a tetanic contraction, not allowing the pt to withdraw from the source and prolonging the duration of contact. AC contact is more ominous than DC contact. AC current = VFIB, DC current can, however, result in asystole.
- Electrical injuries are arbitrarily divided into high-voltage (>600 volts) and low-voltage (<600 volts) burns. Low-voltage burns involve almost exclusively either the hands or oral cavity. High-voltage injuries have a wide variety of systemic manifestations.
- The entry and exit path of the electrical current determines which tissues are affected.

**Treatment**
- At the scene of the injury: ensure that the power source is turned off before approaching.
- Airway-Breathing-CV assessments: respiratory arrest may be prolonged, but prognosis is excellent when breathing is supported.
- Cardiac monitoring
- Oxygen
- Tetanus prophylaxis
- IV fluids to maintain urine output of ≥50 mL/hr (IV hydration should be reassessed w/CNS expert in pts at risk for development of cerebral edema)
- Alkalinization of the urine (sodium bicarbonate 50 mEq in 1 L of NS) in pts w/or at risk of myoglobinuria
- Furosemide 20-40 mg PO or IV and mannitol 12.5 g/kg/hr may be used to force diuresis.
- Seizures are treated in the standard fashion.
- Treat burns w/sulfadiazine silver dressings.
- Hospitalization is indicated in pts w/high-voltage injuries, extensive burns, CNS sx, myonecrosis (CK level >2× nl, ↑ serum myoglobin levels, or myoglobinuria), new cardiac arrhythmia or ECG changes, or any internal organ damage.
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- Ophthalmology consultation at the follow-up to screen for cataract formation (occurs within 1-24 mo after a high-voltage electrical injury in 5%-20% of pts)

**Clinical Pearl**
- PE may not reveal the extent of damage that has occurred. Detailed testing to determine the extent of internal organ damage is indicated. However, in lightning injuries, male victims may suffer from scrotal (on the undersurface of the scrotum) and penile burns, which may often be overlooked. Hemorrhage behind the eardrum w/ or w/o perforation is not uncommon. An otoscopic exam is indicated in all victims struck by lightning.

**143 EMERGENCY CONTRACEPTION (EC)**

**Definition**
Rx women can use to prevent pregnancy soon after unprotected intercourse, sexual assault, or failure or improper use of a birth control method. Options for EC:
- **Plan B**
  - Only FDA-approved product expressly designed for EC available in the U.S.
  - Approved for sale to women and men age ≥17 yr w/o a prescription. Contains the progestin levonorgestrel.
- **Combined oral contraceptives:** higher doses of available oral contraceptive pills containing ethinyl estradiol + levonorgestrel or norgestrel can be used for EC.
- **Copper-bearing intrauterine device (IUD):** emergency insertion of the copper-bearing IUD (Paraguard) can be used for EC, only if pregnancy test is –.
- **Mechanism:** Current evidence indicates that the primary mechanism of Plan B is inhibition of ovulation and that Plan B is not effective after fertilization has occurred. Emergency insertion of the copper IUD may prevent fertilization or subsequent implantation.
- **Effectiveness:** Plan B ↓ the pregnancy rate by 89% after unprotected intercourse. Combined hormonal EC ↓ the risk of pregnancy by about 75%.

**Labs**
- If there is doubt about whether a pt is already pregnant from intercourse that occurred more than a week ago, a pregnancy test may be helpful. However, there is no need for a pregnancy test before administering EC pills. Delays in administration of the medication will ↓ its efficacy. The medications in EC pills will not harm an established pregnancy.

**Treatment**
- Administer EC as soon as possible after unprotected intercourse. EC ↓ the risk of pregnancy when used up to 120 hr (5 days) after unprotected intercourse but is more effective if used earlier.
- **Use of EC:**
  - **Plan B**
    - 2 tablets of 0.75-mg levonorgestrel
    - Both pills can be taken together as a single dose (1.5-mg levonorgestrel). A single dose is equally effective and causes no more side effects than 2 divided doses.
  - **Progestin-only EC pills** are preferable to combined estrogen-progestin EC pills because of ↑ efficacy and ↓ incidence of N/V.
  - **Combined oral contraceptive pills:** 2 doses, 12 hr apart, of 100-120 µg ethinyl estradiol and 0.5-0.6 mg levonorgestrel (or 1.0-1.2 mg norgestrel) per dose.
- **Side effects:** nausea occurs in 50% of women taking combined estrogen-progestin EC pills, vomiting in 20%. Plan B is associated w/about ½ the incidence of N/V. Side effects resolve within 1-2 days. Antinausea medication such as meclizine 25 mg PO is recommended 1 hr before taking combined EC pills.
Contraindications:
- Few contraindications to EC exist other than hypersensitivity to the product. EC will not affect an established pregnancy.
- There are no other evidence-based medical contraindications to the use of EC pills, and very few adverse events have been reported. The benefits of EC in preventing pregnancy generally outweigh the theoretical risks for women who have contraindications to long-term use of combined hormonal contraception, such as thromboembolic disease, smoking after age 35 yr, heart disease, and liver disease. Use of progestin-only EC may be preferable to use of combined estrogen-progestin EC for women w/any of these conditions or who are breastfeeding.
- Alternative EC option: copper IUD. Emergency insertion of the copper IUD is highly effective for EC up to 5 days after unprotected intercourse. This option may be preferable for women who desire effective long-term contraception and have no contraindications to IUD insertion. A pregnancy test should be done before IUD insertion.

Clinical Pearls
- EC is effective in preventing pregnancy up to 120 hr (5 days) after unprotected intercourse.
- A pregnancy test is not necessary before the administration of EC pills because the medications in EC will not harm an existing pregnancy.

144 EMPYEMA

Definition
Accumulation of pus in the pleural space, most often caused by bacterial infection.

Diagnosis

Clinical Presentation

- May be abrupt or chronic and insidious, depending on the etiologic agent and host factors
- Typically presents as progressive pleuritic chest pain, persistent fever, and other sustained signs and sx of infection
- In anaerobic empyema, particularly that caused by the actinomycetes, the clinical picture is dominated by systemic sx and signs: weight loss, malaise, and low-grade fever.
- A slowly enlarging chest wall mass
- As a complication of thoracic trauma or surgery, empyema typically results from contamination of blood within the pleural space several days after the event.
- The physical findings of empyema are those of pleural effusion. ↓ Breath sounds and dullness to percussion over the involved part of the thorax are typical. Systemic signs include fever, tachycardia, leukocytosis, and warmth and erythema over the involved area.

Labs
- CBC, ABGs
- Blood cultures
- Pleural fluid analysis in empyema has the characteristics of an exudate w/a ratio of pleural fluid to serum protein >0.5 or pleural fluid to serum LDH >0.6. Characteristically, empyema fluid is grossly purulent w/visible organisms on Gram stain w/glucose <50 mg/dL and pH <7.

Imaging
- CXR: lateral decubitus view to establish the presence of free fluid in the pleural space
- CT to establish the presence of fluid loculation, underlying mass lesions, and other intrathoracic pathologic processes

Etiology
- Streptococcus pneumoniae
- H. influenzae
- S. aureus
- Legionella species
- *M. tuberculosis*
- *Actinomyces* spp
- A variety of oral anaerobic bacteria have been cultured in 36%-37% of empyemas.

**Treatment**
- Prompt drainage by thoracostomy (chest tube) or open thoracotomy
- Maintenance of drainage until infection controlled
- Abx directed at suspected or proven bacterial or fungal pathogens
- Thoracoscopy or instillation of thrombolytic agents (streptokinase or urokinase) may be considered in refractory, loculated empyema.
- If thorough drainage cannot be accomplished, open thoracotomy w/pleural decortication may be required.
- Lung function should be monitored after completion of Rx.

**Clinical Pearls**
- Empyema caused by actinomycetes may present w/erosion through the chest wall and formation of a fistulous track.
- Nosocomial infection caused by relatively resistant bacterial or fungal pathogens may result in empyema in pts w/indwelling thoracostomy tubes.

### 145 ENCEPHALITIS, ACUTE VIRAL

**Definition**
Acute febrile syndrome w/evidence of meningeal involvement and of derangement of the function of the cerebrum, cerebellum, or brainstem. Can be caused by a host of viruses, w/HSV the most common virus identified.

**Diagnosis**
- **H&P**
  - Clinical presentation: initially, fever and evidence of meningeal irritation w/headache and stiff neck; later, development of signs of cortical dysfunction: lethargy, mental status as coma, stupor, weakness, seizures, facial weakness, and brainstem findings. The presence of classic herpetic skin lesions is suggestive of herpes encephalitis.
- **Labs**
  - LP reveals pleocytosis, usually lymphocytic (although neutrophils may be seen early on), ↑ CSF protein, N/↓ CSF glucose. In herpes simplex encephalitis, RBCs and xanthochromia may be present.
- **Imaging**
  - EEG: periodic high-voltage sharp waves in the temporal regions and slow wave complexes are suggestive of herpes encephalitis.
  - CT scan and MRI: edema and hemorrhage in the frontal and temporal lobes
  - PCR that amplifies DNA from the CSF: useful for herpes simplex encephalitis

**Treatment**
- No specific pharmacologic Rx for most viral pathogens; acyclovir 10 mg/kg every 8 h IV for 14-21 days for herpes simplex encephalitis
- Short courses of corticosteroids to control brain edema and to prevent herniation
- Supportive care, frequent evaluation, and neurologic examination
- Ventilatory assistance for pts who are moribund or at risk for aspiration
- Avoidance of infusion of hypotonic fluids to minimize the risk of hyponatremia
- For pts who develop seizures: anticonvulsant Rx and follow-up in a critical care setting
- For comatose pts: aggressive care to avoid decubiti, contractures, and DVT

### 146 ENCEPHALOPATHY

**Definition**
Clinical syndrome of global cognitive impairment that is characterized by impaired arousal, inattention, and disorientation.
### Diagnosis

**H&P**
- The essential feature of encephalopathy is the pt’s inability to maintain a coherent stream of thought or action.
- The hx may often suggest a waxing and waning of the level of arousal and general cognitive ability.
- Because toxins and metabolic disturbances are common causes of encephalopathy, the hx should focus on exposure to toxins (including medications) and sx suggesting a concurrent illness, such as a UTI or pneumonia.
- Common to all encephalopathies is a fluctuating level of arousal, poor attention, and disorientation.
- Some pts may appear agitated and others lethargic.
- Delusions (fixed false beliefs) and hallucinations are common.
- Asterixis (negative myoclonus) is extremely common.
- Other physical findings depend on the underlying cause of encephalopathy: fever, ascites, jaundice, and tachycardia.

**Labs**
- CBC, lytes, glucose, BUN, Cr, ALT, AST, Ca, B₁₂ level, ammonia, amylase, lipase
- ABGs
- Drug screen and alcohol level
- LP if meningitis, encephalitis, or subarachnoid hemorrhage w/negative imaging is suspected
- HIV (selected pts)
- Endocrine testing: TSH, cortisol level
- U/A, urine C&S

**Imaging**
- CT brain: r/o bleeding, hydrocephalus, tumors
- MRI w/diffusion-weighted images: r/o encephalitis, tumors, and acute strokes
- MRA/venography: r/o arterial dissection, venous thrombosis
- Conventional angiography: CNS vasculitis and aneurysms

### Etiology
- Organ failure (e.g., hepatic encephalopathy, hypoxia, hypercapnia, uremia)
- Infection: systemic (e.g., urinary tract, pneumonia) or involving the CNS (e.g., meningitis, encephalitis)
- Toxin ingestion or withdrawal (e.g., alcohol, medications, recreational drugs)
- Metabolic disturbances: hyperosmolar states, hyponatremia, hypernatremia, hyperglycemia, hypoglycemia, hypercalcemia, hypophosphatemia, acidosis, alkalosis, inborn errors of metabolism
- Endocrinopathy: hyperthyroidism, hypothyroidism, Cushing’s syndrome, adrenal insufficiency, pituitary failure
- Neoplasm: tumors of the CNS, primary or metastatic; also effect of distant tumors (e.g., paraneoplastic limbic encephalitis)
- Nutritional deficiency, mostly in alcoholics and chronically ill pts, such as vitamin B₁₂ deficiency or folate deficiency (Wernicke’s encephalopathy)
- Seizures: postictal state, nonconvulsive status epilepticus, complex partial seizures, absence seizures
- Trauma: concussion, contusion, subdural hematoma, epidural hematoma, diffuse axonal injury
- Vascular: both ischemic and hemorrhagic strokes, vasculitis, venous thrombosis
- Postanoxic encephalopathy
- Others: hypertensive encephalopathy, postoperative, sleep deprivation

### Treatment
- Treat the underlying toxic or metabolic disturbance. The encephalopathy itself is a sx of these underlying problems.
- Glucose IV infusion if hypoglycemia
- Abx in cases of infections (choice of an agent w/good CNS penetration in cases of primary CNS infections)
Diseases can be caused by cells, and platelets. Infective fibrin, inflammatory endocarditis is a condition where the endocardium becomes inflamed. The definition of endocarditis is an infection of the endocardium, which is the lining of the heart. Infections can be caused by bacteria, viruses, fungi, and parasites. The diagnosis of endocarditis usually involves a combination of clinical findings, laboratory tests, and imaging studies. The labs may include blood cultures, complete blood count (CBC), and erythrocyte sedimentation rate (ESR). Imaging studies such as echocardiography (TTE and TEE) are helpful in evaluating the heart for the presence of vegetations or other signs of endocarditis. The etiology of endocarditis can vary depending on the patient’s medical history and the type of infection. Acute endocarditis is usually caused by bacteria such as Staphylococcus aureus, Streptococcus pyogenes, or Escherichia coli, while subacute endocarditis may be caused by viridans streptococci, Enterococcus faecalis, or other organisms. Endocarditis in IV drug users is often caused by Staphylococcus aureus or Pseudomonas aeruginosa. Prosthetic valve endocarditis is a serious complication that can occur after valve replacement surgery. The management of endocarditis includes antibiotic therapy, anticoagulation, and surgical intervention if necessary.
Diseases

- Nosocomial endocarditis: secondary to IV catheters, TPN lines, pacemakers; coagulase-negative staphylococci, *S. aureus*, and streptococci most common
- Non-HACEK gram-negative bacillus endocarditis is not primarily a disease of injection drug users. More than half of all cases are associated w/health care contact.

**Treatment**

Initial IV abx Rx (before culture results) is aimed at the most likely organism:

- Pts w/prosthetic valves or native valves who are allergic to PCN: vancomycin (1 g IV q12h × 4 wk) + rifampin 600 mg PO qd and gentamicin (1 mg/kg IV q8h × 2 wk), assuming nl renal function in adult pts
- IV drug users: nafcillin or oxacillin (2 g IV q4h) + gentamicin (1 mg/kg q8h × 3-5 days until blood cultures are negative); if MRSA, vancomycin (1 g IV q 2h × 4 wk) + gentamicin (1 mg/kg q8h × 3-5 days until blood cultures are negative)
- Native valve endocarditis w/a PCN-susceptible streptococcal isolate: combination of PCN (18-24 million units/day IV × 4 wk) and gentamicin (1 mg/kg q8h × 2 wks), assuming nl renal function. Extend the gentamicin Rx for 4 wk if a relatively PCN resistant strain of streptococcus is isolated (PCN MIC >0.5 µg/mL); a penicillinase-resistant PCN (oxacillin or nafcillin 2 g IV q4h × 4-6 wk + gentamicin 1 mg/kg IV q8h × 3-5 days) can be used if acute bacterial endocarditis is present or if *S. aureus* is suspected as one of the possible causative organisms; for HACEK organisms, treat w/third-generation cep (ceftriaxone 2 g IV q24h × 4-6 wk).
- Ceftriaxone: 2 g IV q4h and an AG (e.g., gentamicin 1 mg/kg IV q8h × 2 wk) effective for *Streptococcus viridans* endocarditis
- Daptomycin (6 mg/kg/day × 4-6 wk): approved for use in *S. aureus* bacteremia and right-sided endocarditis; may prove useful in MRSA infections.
- Abx Rx after identification of the organism should be guided by susceptibility testing, preferably by formal testing by MIC (minimum inhibitory concentration).
- Endocarditis prophylaxis (Table 3-16):
  - Indications:
    - Previous bacterial endocarditis
    - Prosthetic heart valves
    - Unrepaired cyanotic heart disease
  - Procedures: dental procedures only. Prophylaxis is no longer recommended for GI and GU procedures.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Agent</th>
<th>Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard general prophylaxis</td>
<td>Amoxicillin</td>
<td>Adults: 2 g; children: 50 mg/kg PO 1 hr before procedure</td>
</tr>
<tr>
<td>Unable to take oral medications</td>
<td>Ampicillin</td>
<td>Adults: 2 g IM or IV; children: 50 mg/kg IM or IV within 30 min before procedure</td>
</tr>
<tr>
<td>Allergic to penicillin</td>
<td>Clindamycin or Cephalexin¹ or cefadroxil¹ or Azithromycin or clarithromycin</td>
<td>Adults: 600 mg; children: 20 mg/kg PO 1 hr before procedure Adults: 2 g; children: 50 mg/kg PO 1 hr before procedure Adults: 500 mg; children: 15 mg/kg PO 1 hr before procedure</td>
</tr>
<tr>
<td>Allergic to penicillin and unable to take oral medications</td>
<td>Clindamycin or Cefazolin¹</td>
<td>Adults: 600 mg; children: 20 mg/kg IV within 30 min before procedure Adults: 1 g; children: 25 mg/kg IM or IV within 30 min before procedure</td>
</tr>
</tbody>
</table>

*Total children’s dose should not exceed adult dose.

¹Cephalosporins should not be used in individuals with immediate-type hypersensitivity reaction (urticaria, angioedema, or anaphylaxis) to penicillins.
**148 Eosinophilic Fasciitis**

**Definition**
Inflammatory disease of the skin and SC tissue.

**Diagnosis**

**H&P**
- Initial presentation consists of swelling and pain w/ or w/o erythema.
- The extremities are usually symmetrically involved.
- UEs are more commonly affected than LEs.
- The face, fingers, and toes tend to be spared.
- The skin may appear deeply rippled w/an orange peel texture (peau d’orange).
- Sunken veins may be seen when the extremity is elevated.
- The groove sign marks the borders of different muscle groups.
- Arthritis is found in 40% of cases.
- Chronic complications are carpal tunnel syndrome, which was seen in 23% of pts in one series, and flexion contractures.

**Labs**
- Peripheral eosinophilia in up to 70%
- ↑ ESR (29%)
- Hypergammaglobulinemia (35%)
- Occasionally thrombocytopenia and anemia
- Skin bx that penetrates to muscle is optimal for dx.

**Etiology**
- Unclear. A defect in humoral immunity has been hypothesized to cause the disease.
- ↑ Polyclonal IgG levels and immune complexes have been associated w/the disease.

**Treatment**
- Prednisone 1 mg/kg: effective in most pts, but the duration and extent of sx reduction are variable.
- Hydroxychloroquine is an alternative.
- In resistant cases: UVA photochemotherapy, cyclosporine and antithymocyte globulin, MTX, D-penicillamine, and sulfasalazine

**Clinical Pearl**
- Hematologic abnormalities other than eosinophilia are present in 10% of cases; these include aplastic anemia, amegakaryocytic thrombocytopenia, myeloproliferative disorders, myelodysplastic syndrome, leukemia, lymphoma, MM.

**149 Eosinophilic Pneumonias**

**Definition**
Group of disorders characterized by infiltrates on CXR, pulmonary parenchymal eosinophilia, and peripheral blood eosinophilia.

**Diagnosis and Treatment**
Dx varies according to the specific cause of the eosinophilic pneumonia and usually involves a combination of CXR, peripheral eosinophil count, and BAL.

**Simple Pulmonary Eosinophilia (Löffler’s Syndrome)**
- Transient infiltrates
- Sx range from asymptomatic to dyspnea and dry cough
- Usually idiopathic
- May be secondary to parasitic infection or drugs such as nitrofurantoin or PCN
- Rx consists of removal of the offending agent.
- If idiopathic and severe sx, give glucocorticoid Rx.

**Chronic Eosinophilic Pneumonia**
- Idiopathic disease
- Presents w/productive cough, dyspnea, malaise, weight loss, night sweats, and fever
- Progressive peripheral pulmonary infiltrates
- Blood eosinophilia is not always present.
Diseases

Acute Eosinophilic Pneumonia

- Acute onset of cough, dyspnea, fever, tachypnea, and rales
- Pts often require mechanical ventilation.
- Tends to affect the young
- Often blood eosinophilia
- CXR: alveolar infiltrates
- BAL: eosinophils often >20%
- Glucocorticoid Rx often leads to rapid improvement.
- Relapses are rare.
- May be secondary to drugs or cigarette smoking

150 EPIDIDYMIS

Definition

Inflammatory reaction of the epididymis caused by either an infectious agent or local trauma.

Diagnosis

H&P

- Unilateral testicular pain and tenderness; palpable swelling of the epididymis, ↑ warmth

Labs

- Gram-stained smear of urethral exudate or intraurethral swab specimen for N. gonorrhoeae and for NGU (≥5 PMNs per oil immersion field)
- Culture of urethral exudate or intraurethral swab specimen or nucleic acid amplification test (on intraurethral swab or first-void urine) for N. gonorrhoeae
- Exam of first-void urine for leukocytes if the urethral Gram stain is negative. Culture and Gram stain smear of uncentrifuged urine should be obtained.
- VDRL, HIV

Etiology

- Men <35 years of age: N. gonorrhoeae or C. trachomatis
- Homosexuals who are the insertive partners during anal intercourse: E. coli infection
- Non–sexually transmitted epididymitis associated w/UTIs caused by gram-negative enteric organisms: more common among men >35 years of age and among men who have recently undergone urinary tract instrumentation or surgery

Treatment

- Ice packs and scrotal elevation for relief of pain
- Analgesia w/acetaminophen w/ or w/o codeine or NSAIDs
- Abx to cover suspected pathogens
  - In sexually active men: doxycycline 100 mg PO bid × 10 days plus ceftriaxone 250 mg IM as a single dose.
  - Best treatment for older men w/gram-negative bacteriuria: levofloxacin 750 mg PO qd × 10-14 days
  - Pseudomonas: Rx with ciprofloxacin or cefepime (2 g IV q12h)
  - Gentamicin in toxic-appearing pts (1 mg/kg IV q8h after a loading dose of 2 mg/kg): doses must be adjusted for renal function, and these agents may be more toxic.
  - Vancomycin (1 g IV q12h) to cover suspected gram-positive infections
- Surgical aspiration of local abscesses or even open surgical drainage

Clinical Pearls

- Recurrent epididymitis in sexually active men is usually related to failure to simultaneously treat sexual partners for STDs.
- Recurrent epididymitis in non–sexually active men is generally related to structural-anatomic defects in the GU system or relapsing disease from inadequate initial treatment or antimicrobial resistance.
Tuberculous epididymitis fails to respond to seemingly adequate antimicrobial Rx even w/o characteristic radiographic changes on chest films.

151 EPIDURAL HEMATOMA

Definition
Collection of blood between the skull and dura mater.

Diagnosis
H&P
- Lucid interval after the head trauma is followed by progressive reduction in the level of consciousness as the hematoma enlarges and the underlying brain is displaced inward.
- The initial injury causes brain concussion and loss of consciousness from which the pt awakens and may have some headache but seems otherwise to have recovered.
- Downward transtentorial herniation may develop rapidly, causing third nerve compression and an ipsilateral hemiparesis.

Imaging
- Brain CT

Etiology
- Head trauma causing a fx of the squamous portion of the temporal bone and resulting in a tear of the middle meningeal artery
- Neoplasms that have spread into the epidural space

Treatment
- Emergent surgical evacuation

152 EPIGLOTTITIS

Definition
Rapidly progressive cellulitis of the epiglottis and adjacent soft tissue structures w/the potential to cause abrupt airway obstruction.

Diagnosis
H&P
- Irritability, fever, dysphonia, and dysphagia
- Respiratory distress, w/child tending to lean up and forward
- Often, drooling or oral secretions
- Often, presence of tachycardia and tachypnea
- On visualization, edematous and cherry-red epiglottis
- Often, no classic barking cough as seen in croup
- Possibly fulminant course (especially in children), leading to complete airway obstruction

Labs
- CBC: may reveal a leukocytosis w/a shift to the left
- Cultures of blood and urine
- Cultures of the epiglottis (only after establishing adequate airway)

Imaging
- Lateral neck radiograph to show an enlarged epiglottis “thumbprint sign”, ballooning of the hypopharynx, and nl subglottic structures
  - Radiographs are of only moderate sensitivity and specificity and take time to perform.
  - Visualization of the epiglottitis may be safer in adults than in children.
- CXR: evidence of pneumonia in 25% of cases

Etiology
- Children: *H. influenzae* type B
- Adults: *H. influenzae* isolated from blood or epiglottis (26% of cases)
- Pneumococci, streptococci, and staphylococci
- Role of viruses in epiglottitis unclear

Treatment
- Maintenance of adequate airway is critical.
- Early placement of an endotracheal or nasotracheal tube in a child is advised.
Closely observe the adult pt, if no signs of airway obstruction may defer intubation.
- In children, visualization and intubation are best done in the most controlled environment.
- *H. influenzae* incidence in children ↓ because of the Hib vaccine.
- Abx: ceftriaxone (80-100 mg/kg/day in two divided doses), cefotaxime (50-180 mg/kg/day in four divided doses), or ampicillin (200 mg/kg/day in four divided doses) w/chloramphenicol (75-100 mg/kg/day in four divided doses).
- If there is an unvaccinated child at home (or in a daycare center) who is <4 yr and living w/ index case, give close family contacts of the pt (including adults) rifampin 20 mg/kg/day for 4 days (up to 600 mg/day) for prophylaxis.
- Role of epinephrine or corticosteroids in the management of epiglottitis is not firmly established.

**153 ERYSIPELAS**

**Definition**
Type of cellulitis caused by infection of the superficial layers of the skin and cutaneous lymphatics.

**Diagnosis**
- Distinctive red, warm, tender skin lesion w/ induration and a sharply defined, advancing, raised border is present.
- Most common sites are LEs or face.
- Systemic signs of infection (fever) are often present.
- Vesicles or bullae may develop.
- After several days, lesions may appear ecchymotic.
- After 7-10 days, desquamation of affected area may occur.

**Etiology**
- Usually group A beta-hemolytic streptococci
- Less often group B, C, or G streptococci
- Rarely *S. aureus*

**Treatment**
- Typical erysipelas of extremity in nondiabetic pt:
  - PO: PCN V K 500 mg qid × 10 days
  - IV: PCN G (aqueous) 1-2 million units q6h
  - Note: use erythromycin or cephalin in pts allergic to PCN.
- Facial erysipelas (include coverage for *S. aureus*):
  - PO dicloxacillin 500 mg q6h
  - IV nafcillin or oxacillin 2 g q4h

**154 ERYTHEMA MULTIFORME**

**Definition**
Inflammatory disease believed to be secondary to immune complex formation and subsequent deposition in the skin and mucous membranes.

**Diagnosis**
- Symmetric skin lesions w/classic “target” appearance (caused by the centrifugal spread of red maculopapules to circumference of 1-3 cm w/a purpuric, cyanotic, or vesicular center) are present.
- Lesions are most common on the back of the hands and feet and extensor aspect of the forearms and legs. Trunk involvement can occur in severe cases.
- Urticarial papules, vesicles, and bullae may also be present and generally indicate a more severe form of the disease.
- Individual lesions heal in 1-2 wk w/o scarring.
- Bullae and erosions may also be present in the oral cavity.

**Treatment**
- Mild cases generally do not require treatment; lesions resolve spontaneously within 1 mo.
Potential drug precipitants (e.g., PCN, bupropion) should be removed. 
Treatment of associated diseases (e.g., acyclovir for herpes simplex, erythromycin for *Mycoplasma* infection) 
Prednisone 40-80 mg/day for 1-3 wk: in pts w/many target lesions; however, the role of systemic steroids remains controversial. 
Lefamisole, an immunomodulator, may be effective in treatment of pts w/chronic or recurrent oral lesions (dose is 150 mg/day × 3 consecutive days used alone or in combination w/prednisone).

**Clinical Pearl**

The rash of erythema multiforme generally evolves during a 2-wk period and resolves within 3-4 wk w/o scarring. A severe bullous form can occur (see *Stevens-Johnson Syndrome*).

### 155 ERYThema NODosum

**Definition**

Acute, tender, erythematous, nodular skin eruption resulting from inflammation of SC fat, often associated w/bruising.

**Diagnosis**

*H&P*

- Acute onset of tender nodules typically located on shins, occasionally seen on thighs and forearms
- The nodules are usually \( \frac{1}{2} \) inch in diameter but can be as large as 4 inches; they begin as light red lesions, then become darker and often ecchymotic. The nodules heal within 8 wk w/o ulceration.
- Associated findings: fever, lymphadenopathy, arthralgia

**Labs**

- ↑ ESR, throat C&S, ASO titer, PPD

**Imaging**

- CXR: r/o sarcoidosis, TB

**Etiology**

- Cell-mediated hypersensitivity reaction seen more frequently in pts w/HLA antigen B8. The lesion results from an exaggerated interaction between an antigen and cell-mediated immune mechanisms, leading to granuloma formation.
- May be secondary to infections, drugs, sarcoidosis, cancer (usually lymphoma), ankylosing spondylisis, and reactive arthropathies (e.g., associated w/IBD)

**Treatment**

- NSAIDs for pain
- Systemic steroids in severe cases

### 156 ESSENTIAL TREMOR

**Definition**

Predominantly postural and action tremor that is bilateral and tends to progress slowly during the years in the absence of other neurologic abnormalities.

**Diagnosis**

- Pts complain of tremor that is most bothersome when writing or holding something, such as a newspaper, or trying to drink from a cup; worsens under emotional duress and is made better w/alcohol ingestion.
- Tremor, 4-12 Hz, bilateral postural and action tremor of the UEs; may also affect the head, voice, trunk, and legs; typically is the same amplitude throughout the action, such as bringing a cup to the mouth. No other neurologic abnormalities on examination.
- Table 3-17 shows diff dx.

**Etiology**

- Often an inherited disease, autosomal dominant; sporadic cases w/o a FHx are frequently encountered.
**Chapter 3  Diseases and Disorders**

**ETHANOL POISONING**

**Diagnosis**

_H&P_

- Alcohol inhibits the conversion of lactate to glucose in the liver. Alcoholic ketoacidosis usually follows binge drinking.
- Abd pain, vomiting, starvation, volume depletion

_Labs_

- AG metabolic acidosis
- ↑ Osmolal gap (difference between the measured and calculated serum osmolality)
- N/↓ blood glucose
- ↑ BUN, Cr, hypophosphatemia, hypokalemia, hypomagnesemia

**Treatment**

- Volume repletion, thiamine and glucose administration
- Correction of hypophosphatemia, hypokalemia, and hypomagnesemia if present

**Clinical Pearl**

- Metabolic acidosis is also associated with ingestion of ethylene glycol and methanol in addition to ethanol. Direct measurement of these should be performed whenever possible.

**158 ETHYLENE GLYCOL, ISOPROPYL ALCOHOL, AND METHANOL POISONING**

**Diagnosis**

_H&P_

- Ethylene glycol is a component of antifreeze and industrial solvents. It has a sweet taste and may be ingested accidentally or in suicide attempts.
- Methanol is a component of wood alcohol (moonshine liquor), copy machines, embalming fluid, paint removers, and windshield wiper fluid.
- Isopropyl alcohol is found in rubbing alcohol.
Chapter 3  Diseases and Disorders

- CNS sx (lethargy, seizures, coma), renal failure, pulmonary, cardiac failure
- Dehydration
- Optic papillitis leading to blindness from metabolism of methanol to formaldehyde and formic acid

**Labs**
- AG acidosis in ethylene glycol and methanol poisoning. Isopropyl alcohol does not cause ↓ AG or ketoacidosis because the metabolite is acetone, but test results are positive for ketones.
- ↓ Osmolal gap (difference between the measured and calculated serum osmolality)
- Ca oxalate crystals in the urine in ethylene glycol poisoning

**Treatment**
- Competitive inhibition of alcohol dehydrogenase w/fomepizole (preferred) or ethanol (when fomepizole is not available) and hemodialysis (in all cases when ethanol is used as Rx and in fomepizole Rx and profound acidemia and signs of optic or renal injury).
- Criteria for initiation of Rx: ethylene glycol plasma concentration ≥20 mg/dL (3.2 mmol/L) or methanol plasma concentration ≥20 mg/dL (6.2 mmol/L); suspected ethylene glycol or methanol ingestion and ≥ 2 of the following criteria: arterial pH <7.3, Osmo gap >10 mOsm/L, serum carbon dioxide level <20 mmol/L
- Dosing of fomepizole:
  - Pts not undergoing hemodialysis: loading dose is 15 mg/kg BW, followed by 10 mg/kg q12h; after 48 hr, 15 mg/kg q12h.
  - Pts undergoing hemodialysis use same dose except that drug is given 6 hr after the first dose and q4h thereafter.
  - Continue fomepizole Rx until the plasma ethylene glycol or methanol concentration is <20 mg/dL.
- IV rehydration in all pts; sodium bicarbonate administration in pts w/pH <7.3
- In methanol poisoning, administer folic acid (leucovorin) 1 mg/kg BW IV (up to 50 mg) or stereospecific levoleucovorin at 1/3 dose of leucovorin. The administration of folate is beneficial because formic acid is catabolized to CO₂ and water by tetrahydrofolate synthetase (enzyme dependent on stored folate).
- Pyridoxine may be beneficial in ethylene glycol poisoning (pyridoxine is a cofactor in metabolism of glycolic acid to glycine).

**Clinical Pearls**
- The CNS dysfunction is primarily due to the keto aldehyde metabolites.
- Intratubular obstruction and ARF may be due to oxalate crystals in ethylene glycol poisoning.

### 159 EUTHYROID SICK SYNDROME

**Definition**
Alteration in TSH secretion and thyroid hormone peripheral binding and metabolism secondary to severe nonthyroidal illness or stress.

**Labs**
- ↑ Reverse T₃, ↓ T₃ RIA
- Free T₄ is nl in early stage, ↑ in stage 2, and ↓ in stage 3.
- Thyrotropin is nl except in stage 3 (↓)

**Etiology**
- Suppression of pituitary hormone release, which is either endogenous (due to loss of hypothalamic input) or worsened by some agents (e.g., glucocorticoids) often given to very ill pts

### 160 FELTY’S SYNDROME (FS)

**Definition**
Triad of RA, splenomegaly, and granulocytopenia.

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*Brent J: NEJM 360:21, 2009.*
**Diseases**

**FEVER AND NEUTROPENIA**

by

H&P

**Diagnosis**

- Rarely, splenomegaly and granulocytopenia are present before the arthritis.
- Articular involvement is usually more severe in pts w/FS compared with other pts w/RA; however, $f$ may have relatively inactive synovitis w/$\uparrow$ ESR.
- Degree of splenomegaly varies and may be detectable only by imaging studies.
- The degree of splenomegaly has no correlation w/the degree of granulocytopenia.
- FS pts have $>^{\text{frequency}}$ of extra-articular manifestations (nodules, weight loss, Sjögren’s syndrome) than do other pts w/RA.
- Approximately 25% of pts have refractory leg ulcers, often associated w/hyperpigmentation of the anterior tibia.
- Mild hepatomegaly is common (up to 68%).

**Labs**

- CBC w/diff: granulocytopenia, mild to moderate anemia, mild thrombocytopenia
- Bone marrow bx: myeloid hyperplasia w/excess immature granulocyte precursors (“maturation arrest”)
- Other labs: RF (+ in 98%, usually high titer), ANA (+ in 67%), antihistone Ab (+ in 83%), antineutrophil cytoplasmic Abs (+ 77%), HLA-DR4 (+ in 95%)

**Treatment**

- MTX
- Corticosteroids
- Others: recombinant granulocyte colony-stimulating factor; limited experience w/cyclophosphamide, cyclosporine, azathioprine, leflunomide, anti–TNF-α Ab, and rituximab
- Splenectomy
  - Usually reserved for pts w/profound neutropenia (<1000/mm$^3$) and severe recurrent infections
  - Acutely reverses hematologic abnormalities
  - 25%-30% will have recurrent neutropenia, but the granulocyte count usually remains above the presplenectomy level.

**Clinical Pearl**

- Pts w/FS have a 20× $\uparrow$ frequency of infections compared with other RA pts.

### 161 FEVER AND NEUTROPENIA (INFECTIONS IN THE IMMUNOCOMPROMISED HOST)

**Definition**

An immunocompromised host is one whose resistance to infection is impaired by an underlying disease or by immunosuppressive Rx.

**Diagnosis**

H&P

- The clinical manifestations may be greatly modified or masked by the underlying illness:
  - The pt may not be able to mount a fever response or a leukocytosis.
  - Pulmonary infiltrates in pulmonary infections may be absent or slow to develop because of leukopenia.
  - The clinical findings may be minor (e.g., mild headache w/o meningismus in pts w/cryptococcal meningitis; deep-seated abscesses w/o evidence of inflammation).
- Hx:
  - Recent use of abx, corticosteroids, chemotherapeutic agents, and radiotherapy
  - H/o recurrent infections, recent travel, and exposure to contagious diseases
  - H/o bone marrow transplantation (CMV, varicella-zoster, parasitic or fungal infections) or solid organ transplantation (CMV, EBV), splenectomy ($S. \ pneumoniae$)
Chapter 3  Diseases and Disorders

- **PE:**
  - Presence of skin lesions
    - Ecthyma gangrenosum: embolic skin manifestations of gram-negative bacilli; usually begins as a red macule (0.5–3 cm in diameter), then becomes more papular w/central necrosis of vesicle formation surrounded by erythema.
    - Mucormycosis: usually seen in diabetic pts; manifested as a black eschar on the palate and nasal passages.
  - Evidence of fungal colonization (oropharynx, rectum, vagina)
  - Evaluate mental status; look for evidence of meningismus or focal deficits.
  - Auscultate the heart for presence of new murmurs or accentuation of an existing murmur (suggestive of bacterial endocarditis), particularly in IV drug users and pts w/central lines in place.
  - Evidence of respiratory infection (↓ breath sounds, rales, rhonchi); the lungs are the most frequent site of infection in immunocompromised pts.
  - Evaluate areas that may “hide” an infection, such as the oral cavity and the perineal area.

- **Labs**
  - CBC w/diff
  - U/A, urine C&S, and Gram stain
  - Blood cultures (at a minimum, two sets should be obtained); if the pt has an indwelling IV catheter, at least one set should be drawn through the catheter; in pts w/multilumen catheters, consider obtaining a culture specimen through each lumen and label the culture bottle.
  - Sputum Gram stain, AFB stain, and cultures
  - C&S and Gram stain of any suspicious skin lesions (e.g., lesion expressing pus)
  - Routine LP is not recommended, especially in the presence of thrombocytopenia.

- **Imaging**
  - CXR: infiltrates, lobar consolidation, cavitary lesions

- **Treatment**
  - Management should be guided by the nature of the host-defense defects.
  - Rx w/AG and a β-lactam (e.g., tobramycin 2 mg/kg IV q8h + piperacillin 50 mg/kg IV q4h) can be used. The combination of ciprofloxacin 400 mg IV q8h and piperacillin 50 mg/kg IV q4h is also effective and less nephrotoxic.
  - Pts w/neutropenia of 10 days’ duration or less, those w/solid tumors, and those who have received less intensive chemotherapy regimens generally have a lower risk and may be initially treated w/single parenteral agent (e.g., ceftazidime, imipenem, meropenem, cefepime) or combination oral Rx (ciprofloxacin and amoxicillin-clavulanate) ± vancomycin, depending on indications.
  - Empiric antifungal Rx of pts w/neutropenia and persistent fever is commonly used to cover invasive fungal infections, especially infection w/C. albicans. Antifungal Rx, however, is not recommended for the initial treatment in the neutropenic pt. It is recommended after 3–5 days of fever on empiric abx. Voriconazole, an antifungal triazole, and caspofungin are effective agents. Conventional empiric antifungal Rx w/ampphotericin is frequently associated w/nephrotoxicity, pulmonary toxicity, and infusion-related toxic effects.

162 **FEVER OF UNDETERMINED ORIGIN (FUO)**

- **Definition**
  Illness characterized by temp >101°F on several occasions for >3 wk w/no known cause despite extensive w/u.

- **Diagnosis**
  - **H&P**
    - Hx clues:
      - Fever duration, tempo; inciting factors
      - Associated sx: rash, myalgia, weight loss, pain
      - Sick contacts
• PMHx: HIV infection, malignant neoplasms, surgeries
• Medications
• FHx: tuberculosis in a relative, malignant neoplasms, familial Mediterranean fever
• SHx: daily routine, rural vs. urban, pets and animal contacts, arthropod bites, travel—recent and remote, socioeconomic status, occupation, military service, sexual hx

- Physical findings:
  - HEENT: r/o sinusitis, dental abscesses; examine eyes carefully.
  - Neck: check for adenopathy.
  - Lungs: auscultate for rales.
  - Heart: listen for murmur.
  - Abd: check for organomegaly.
  - Rectal: examine for prostate tenderness/mass.
  - Pelvic: r/o cervical motion tenderness; check for inguinal adenopathy.
  - Extremities: look for clubbing, splinter hemorrhages; examine IV access site.
  - Musculoskeletal: examine for joint effusions.
  - Skin: note any rashes, wounds.

- Labs
  - Base on hx clues and physical findings: blood cultures, CBC, U/A, transaminases; PPD testing is important in most FUO workups.
  - Base on leads from hx, examination—whether need for serum Ab testing, LP, thyroid function testing, stool culture and C. difficile assay, bone marrow bx, skin bx, ANA. Laboratory examinations may need to be repeated at regular intervals until dx is established.

- Imaging
  - Base on hx clues and physical findings. CXR, abd CT are important eventually in most workups where dx is elusive.

- Etiology
  - Classic (1 wk w/u after 2 wk persistently febrile): divided into infection, malignant disease, collagen-vascular, and other etiology; proportion for each dependent on age, geography, host and microbial factors, hospital and health services. Etiology has also changed over time. A partial list of eventual causes, w/most common diagnoses in italics:
    - Factitious fever, Munchausen syndrome
    - Abscess: dental, abd, pelvic
    - Lymphoma and leukemia
    - Endocarditis (especially caused by difficult-to-isolate organisms)
    - Biliary tract infection
    - Osteomyelitis
    - TB
    - Whipple’s disease
    - Psittacosis
    - Fungal: histoplasmosis, cryptomycosis
    - Leishmaniasis
    - Renal cell carcinoma, other solid malignant neoplasms
    - SLE
    - Still’s disease
    - Hypersensitivity vasculitis
    - Giant cell arteritis
    - Drug-induced fever
    - IBD
    - Sarcoidosis
    - Granulomatous hepatitis
    - Central fever (rare)
  - Neutropenic (PMN <500 and febrile >3 days): w/blood cultures from onset negative, ruling out Pseudomonas and other gram-negative bacteremia, staphylococcal bacteremia from line infection; U/A and CXR negative. Possible causes:
    - Perianal infection
    - Occult fungal infection
• Drug fever
• CMV infection in post-transplantation pts or pts who are on immunosuppressants.

**HIV-associated**: etiology depends on CD4 count. HIV infection itself may be the cause. W/low CD4 count: *Mycobacterium avium-intracellulare* bacteremia, non-Hodgkin’s lymphoma.

**Nosocomial** (febrile for 3 days in hospital): UTI, pneumonia, line-related bacteremia, *C. difficile* diarrhea, or sinusitis secondary to intubation

**Noninfectious etiology**: DVT, hematoma, drug fever

**Treatment**

• Abx and other treatment are indicated only after definitive or highly probable ID dx is established, unless pt appears severely ill or septic.

**Clinical Pearls**

• When in doubt, perform another complete H&P.
• Persistence for >2 wk usually separates a FUO from an insignificant viral illness.

163 **FOLLICULITIS**

**Definition**

Inflammation of the hair follicle as a result of infection, physical injury, or chemical irritation.

**Diagnosis**

**H&P**

• Lesions generally consist of painful yellow pustules surrounded by erythema; a central hair is present in the pustules.

• Sycosis barbae may initially present w/small follicular papules or pustules that ↑ in size w/continued shaving; deep follicular pustules may occur surrounded by erythema and swelling; the upper lip is frequently involved.

• “Hot tub” folliculitis occurs within 1-4 days after use of hot tub w/poor chlorination. It is characterized by pustules w/surrounding erythema generally affecting torso, buttocks, and limbs.

**Labs**

• Gram stain is useful to identify the infective organisms in infectious folliculitis and to differentiate infectious folliculitis from noninfectious.

**Etiology**

• *Staphylococcus* infection (e.g., sycosis barbae), *P. aeruginosa* (“hot tub” folliculitis)

• Gram-negative folliculitis (*Klebsiella, Enterobacter, Proteus*) associated w/abx Rx of acne

• Chronic irritation of the hair follicle (use of cocoa butter or coconut oil, chronic irritation from workplace)

• Initial use of systemic corticosteroid Rx (steroid acne), eosinophilic folliculitis (AIDS pts), *C. albicans* (immunocompromised pts)

• *Pityrosporum orbiculare*

**Treatment**

• Cleanse affected area w/chlorhexidine and apply saline compresses.

• Apply 2% mupirocin ointment for bacterial folliculitis affecting a limited area (e.g., sycosis barbae).

• *Pseudomonas* folliculitis: ciprofloxacin 500 mg bid × 10 days

• *S. aureus* folliculitis: dicloxacillin 250 mg qid × 10 days

• Chronic nasal or perineal *S. aureus*: rifampin 300 mg bid × 5 days.

Mupirocin ointment 2% applied to nares bid is also effective for nasal carriers.

**Clinical Pearls**

• Steroid folliculitis responds to discontinuation of steroids.

• Pts should be instructed in good personal hygiene and avoidance of sharing razors, towels, and washcloths.
164 FRIEDREICH’S ATAXIA

Definition
Most common neurodegenerative hereditary ataxic disorder, caused by degeneration of dorsal root ganglions, posterior columns, spinocerebellar and corticospinal tracts, and large sensory peripheral neurons.

Diagnosis
H&P
- Onset of progressive appendicular and gait ataxia, w/absent muscle stretch reflexes in the LEs
- W/disease progression (within 5 yr): dysarthria, distal loss of position and vibration sense, pyramidal leg weakness, areflexia in all 4 limbs, extensor plantar responses
- Common findings: progressive scoliosis, distal atrophy, pes cavus, and cardiomyopathy (symmetric concentric hypertrophic form in most cases)
- Electrophysiologic testing: diagnostic criteria include electrophysiologic evidence for a generalized axonal sensory neuropathy.

Labs
- Sural nerve bx shows major loss of large myelinated fibers.
- Specific gene testing for the expanded GAA trinucleotide repeat

ECG
- ECG shows widespread T wave inversion and evidence of LVH in 65% of pts.

Etiology
- Genetic: frataxin gene is localized to the centromeric region of chromosome 9q13.
- NI sequence has 6-27 repeats; abnl sequence has 120-1700 GAA repeats.
- Frataxin deficiency leads to impaired mitochondrial iron homeostasis.

Treatment
- Surgical correction of scoliosis and foot deformities in selected pts
- Prosthetic devices as required (e.g., ankle-foot orthosis for footdrop)
- Physical Rx
- Communication devices for pts w/severe dysarthria
- An antioxidant, idebenone (short-chain analogue of coenzyme Q10), administered PO at 5-10 mg/kg/day w/ or w/o vitamin E, may improve outcomes in pts w/cardiomyopathy w/o clinical deterioration.
- Chronic management of CHF
- Cardiac arrhythmias may warrant pacemaker implantation.

Clinical Pearls
- DM may occur in 10% of pts, w/glucose intolerance occurring in an additional 10%-20%.
- Loss of ambulation typically occurs within 15 yr of sx onset, and 95% are wheelchair bound by age 45 yr.
- Life expectancy is ↓, particularly if heart disease w/ or w/o DM is present. Mean survival from sx onset is 36 yr.

165 FROSTBITE

Definition
Tissue injury (or death) from freezing and vasoconstriction induced by severe environmental cold exposure.

Diagnosis
H&P
- Frostbite may be classified into grades I to IV of injury severity or, more practically, into superficial and deep groups.
- Superficial frostbite involves the skin and SC tissue. The frozen part is waxy, white, and firm but soft and resilient below the surface when gently depressed. After rewarming, the frostbitten area may appear mottled and swollen, and superficial blisters w/clear or milky fluid may form within 6-24 hr. There is no ultimate tissue loss.
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- Deep frostbite also involves muscles, nerves, tendons, or bones. The skin may be hard or wooden, w/o tissue resilience. Edema, nonblanching cyanosis, hemorrhagic blisters (after 3–7 days), tissue necrosis, and gangrene may develop. Affected tissue has a poor prognosis, and debridement or amputation is generally required.
- Pts initially experience numbness, pricking, and itching. More severe injury can produce paresthesias and stiffness, w/burning or throbbing pain on thawing.

Labs
- Lab work is not indicated unless pt has systemic hypothermia.

Imaging
- No reliable predictors of tissue viability. Technetium scintigraphy, MRI, and MRA are the most promising. (Some centers perform technetium scintigraphy or angiography within 24 hr and give thrombolitics to those w/impaired blood flow.)

Etiology
Two mechanisms of tissue injury:
- Cellular death occurring at time of exposure from intracellular water crystallization and temperature-induced protein changes
- Vascular impairment from vasoconstriction, endothelial injury, and associated thrombosis as a result of tissue thawing and associated edema. Most frostbite injury occurs in this phase. Hemorrhage, necrosis, and gangrene may develop.

Treatment
- Remove constricting/wet clothing. Gently insulate, splint, elevate affected area.
- If hypothermic (core body temperature <32°C), initiate active core rewarming (e.g., pleural and peritoneal irrigation, hemodialysis, or cardiopulmonary bypass) and adjunctive treatment w/warmed, humidified oxygen, heated IV saline (45°C), and warming blankets before thawing of frostbitten extremities.
- Rapid rewarming is the main objective.
- Immerse affected area in circulating warm water bath w/a mild antibacterial agent (e.g., hexachlorophene or povidone–iodine) maintained at 40°C–42°C for 15–30 min. Repeat until capillary refill returns and tissue is supple and flushed. Active motion during rewarming is advisable, massage is not. Blisters should be kept intact to protect skin from infection.
- IV narcotics for pain during thawing
- Td prophylaxis and topical abx if potentially contaminated skin wound
- Streptococcal prophylaxis for 48–72 hr w/IV PCN for severe cases
- Thrombolytic Rx followed by short-term anticoagulation appears to considerably improve reperfusion and ↓ predicted digit amputations. Tissue plasminogen activator improves tissue perfusion and ↓ amputations when administered within 24 hr of injury.
- Pentoxifylline may be effective in preventing further tissue loss.
- Dextran, vasodilators, hyperbaric oxygen, reserpine, and sympathectomy are of unproven benefit.

Post-Thaw Rx
- Daily dressing changes w/dry, sterile, noncompressive, and nonadherent dressings. Splint and elevate hands and feet to ↓ edema and separate digits w/cotton gauze. Avoid even slightest abrasion; prevention of infection is highly important.
- Whirlpool hydrotherapy w/warm water (38°C) and an antiseptic for 20–30 min bid-tid for several weeks
- Debride broken clear vesicles and avoid disrupting intact blisters (especially hemorrhagic ones) unless they interfere w/mobility.
- Topical aloe vera q6h and ibuprofen 400–600 mg tid for 1 wk may be beneficial as thromboxane inhibitors.
- Gentle, progressive physical Rx after edema resolves
- Avoid all vasoconstrictors, including nicotine.
**Clinical Pearls**
- Avoid thawing if any risk of refreezing.
- Never rub or massage the affected area. Avoid dry heat (e.g., fires, heaters) and exercising the affected area.

**166 GARDNER’S SYNDROME**

**Definition**
Variant of familial adenomatous polyposis (FAP), w/prominent extraintestinal manifestations. It is an autosomal dominant condition characterized by:
- Adenomatous intestinal polyps
- Soft tissue tumors
- Osteomas

**Diagnosis**
- In individuals w/ a FHx, dx is confirmed by ≥100 adenomatous polyps in the colon, >3 pigmented ocular lesions on funduscopic examination, or genetic testing.
- There is phenotypic variability even in families w/same mutation. Soft tissue and bone abnormalities may precede intestinal disease.
- Congenital hypertrophy of the retinal pigment epithelium (often the first sign) is diagnosed by ophthalmologic examination.
- Dental abnormalities: supernumerary teeth, unerupted teeth
- Soft tissue lesions: epidermoid cysts, sebaceous cysts, fibromas, lipomas, desmoid tumors
- Bone abnormalities of skull, mandible, and long bones
- Abd mass, OB + stool

**Etiology**
- Caused by mutations of the adenomatous polyposis coli (APC) gene on chromosome 5q21. >300 mutations of the APC gene have been identified. The site of the mutation may explain the extraintestinal lesions that differentiate Gardner’s syndrome from other variants of FAP.
- Spontaneous mutations are responsible for 20%-40% of FAP cases.

**Treatment**
- Colectomy is recommended once polyps are seen on colonoscopy.
- Regular screening of remaining GI tract and extraintestinal manifestations must continue after colectomy.

**Clinical Pearls**
- Polyps occur at a mean age of 16 yr.
- Cancer develops in 7% of individuals by age 21 yr, 50% by age 39 yr, and 90% by age 45 yr.

**167 GASTRITIS**

**Definition**
Histologically, gastritis refers to inflammation in the stomach. Endoscopically, gastritis refers to a number of abnl features, such as erythema, erosions, and subepithelial hemorrhages. Gastritis can also be subdivided into erosive, nonerosive, and specific types of gastritis w/distinctive features both endoscopically and histologically.

**Diagnosis**

**H&P**
- Pts w/gastritis generally present w/nonspecific clinical signs and sx (e.g., epigastric pain, Abd tenderness, bloating, anorexia, nausea [w/ or w/o vomiting]). Sx may be aggravated by eating. Diagnostic w/u includes a comprehensive hx and endoscopy w/bx.

**Labs**
- *H. pylori* testing by urea breath test, stool antigen test (*H. pylori* stool antigen), endoscopic bx, or specific Ab test is recommended:
  - The urea breath test documents active infection (sensitivity and specificity >90%).
• Stool antigen test is as accurate as the urea breath test for dx of active infection and follow-up evaluation of pts treated for H. pylori. A negative result on the stool antigen test 8 wk after completion of Rx identifies pts in whom eradication of H. pylori was unsuccessful.
• Serologic testing for Ab to H. pylori: presence of Ab demonstrates previous but not necessarily current infection. Ab to H. pylori can remain ↑ for months to years after infection has cleared; therefore, Ab levels must be interpreted in light of pt’s sx and other test results (e.g., PUD seen on UGI series).
  - Vitamin B₁₂ level in pts w/atrophic gastritis
  - Hct (↓ if significant bleeding has occurred)

**Etiology**
- Alcohol, NSAIDs, stress (critically ill pts usually on mechanical respiration), hepatic or renal failure, multiorgan failure
- Infection (bacterial, viral)
- Bile reflux, pancreatic enzyme reflux
- Gastric mucosal atrophy, portal HTN gastropathy
- Irradiation

**Treatment**
Eradication of H. pylori with
  - PPI bid plus clarithromycin 500 mg bid and amoxicillin 1000 mg bid for 7-10 days
  - PPI bid plus amoxicillin 500 mg bid plus metronidazole 500 mg for 7-10 days
  - PPI bid plus clarithromycin 500 mg bid and metronidazole 500 mg bid for 7 days
  - Lifestyle modifications w/avoidance of tobacco, alcohol, NSAIDs and foods that trigger sx

**GASTROESOPHAGEAL REFLUX DISEASE (GERD)**

**Definition**
Motility disorder characterized primarily by heartburn and caused by the reflux of gastric contents into the esophagus.

**Diagnosis**

**H&P**
- Clinical signs and sx: heartburn, dysphagia, sour taste, regurgitation of gastric contents into the mouth, chronic cough and bronchospasm, chest pain, laryngitis, early satiety, abd fullness and bloating w/belching, dental erosions in children

**EGD and Additional Testing**
- Useful to document the type and extent of tissue damage in GERD and to exclude potentially malignant conditions such as Barrett’s esophagus
- 24-hr esophageal pH monitoring and Bernstein test: not very practical and generally not done. They are useful in pts w/atypical manifestations of GERD, such as chest pain and chronic cough.
- Esophageal manometry: indicated in pts w/refractory reflux in whom surgical Rx is planned.
- Upper GI series can identify ulcerations and strictures; however, it may miss mucosal abnormalities. Only ¼ of pts w/GERD have radiographic signs of esophagitis.

**Etiology**
- Incompetent LES
- Medications that ↓ LES pressure (CCBs, β-adrenergic blockers, theophylline, anticholinergics)
- Foods that ↓ LES pressure (chocolate, yellow onions, peppermint)
- Tobacco abuse, alcohol, coffee
- Pregnancy
- Gastric acid hypersecretion
- Hiatal hernia (controversial) present in >70% of pts w/GERD; however, most pts w/hiatal hernia are asymptomatic.
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**GENITAL HERPES**

**Definition**

Viral infection caused by HSV. HSV-1 is associated primarily w/oral infections, whereas HSV-2 causes mainly genital infections; however, each type can infect any site. After the primary infection, the virus enters the nerve endings in the skin directly below the lesions and ascends to the dorsal root ganglia, where it remains in a latent stage until it is reactivated.

**Diagnosis**

**H&P**

- **Primary infection:**
  - Sx occur 3–7 days after contact
  - Constitutional sx include low-grade fever, headache and myalgias, regional lymphadenopathy, and localized pain.
  - Pain, burning, itching, and tingling last several hours.
  - Grouped vesicles usually w/surrounding erythema appear and generally ulcerate or crust within 48 hr.
  - The vesicles are uniform in size (differentiating it from herpes zoster vesicles, which vary in size).
  - During the acute eruption, the pt is uncomfortable; urinary retention may occur in severe cases.
  - Lesions generally last 2–6 wk and heal w/o scarring.

- **Recurrent infection:**
  - Generally caused by alteration in the immune system; fatigue, stress, menses, local skin trauma
  - The prodromal sx (fatigue, burning and tingling of the affected area) last 12–24 hr.
  - A cluster of lesions generally evolves within 24 hr from a macule to a papule and then vesicles surrounded by erythema; the vesicles coalesce and subsequently rupture within 4 days, revealing erosions covered by crusts.
  - The crusts are generally shed within 7–10 days, revealing a pink surface.
  - The most frequent location of the lesions is on the penile shaft or glans penis and the labia (HSV-2).

**Labs**

- DFA slide tests will provide a rapid dx.
- Viral culture is the most definitive method for dx; results are generally available in 1–2 days; the lesions should be sampled during the vesicular or early ulcerative stage; cervical samples should be taken from the endocervix w/a swab.
- Pap smear will detect HSV-infected cells in cervical tissue from women w/o sx.

**Treatment**

- Lifestyle modifications w/avoidance of foods (citrus- and tomato-based products) and drugs that exacerbate reflux (e.g., caffeine, β-blockers, CCBs, α-adrenergic agonists, theophylline)
- Avoidance of tobacco and alcohol use
- Elevation of head of bed 4–8 inches with blocks
- Avoidance of lying down directly after late or large evening meals
- Weight reduction, ↓ fat intake
- Avoid wearing clothing that is tight around the waist
- PPIs: preferred Rx
- H₂ blockers: less effective than PPIs
- Antacids: may be useful for relief of mild sx; however, they are generally ineffective in severe cases of reflux.
- Prokinetic agents (metoclopramide): indicated only when PPIs are not fully effective. They can be used in combination Rx; however, side effects limit their use.
- Nissen fundoplication: for refractory cases
- Endoscopic radiofrequency heating of the gastroesophageal junction (Stretta procedure) is a newer treatment modality for GERD pts unresponsive to traditional Rx.
Serologic tests for HSV: IgG and IgM serum Abs. Abs to HSV occur in 50%-90% of adults. Routine tests do not discriminate between Abs that are HSV-1 and HSV-2; the presence of IgM or a 4-fold or greater rise in IgG titers indicates a recent infection (convalescent sample should be drawn 2-3 wk after the acute specimen is drawn).

**Treatment**

- Acyclovir ointment or cream applied with finger-cot or rubber glove q3-6h (6× qd) × 7 days may be useful for the first clinical episode of genital herpes. Severe primary genital infections may be treated w/IV acyclovir (5 mg/kg infused at a constant rate during 1 hr q8h × 7 days in pts w/nl renal function) or oral acyclovir 200 mg 5 times qd × 10 days.
- Valacyclovir caplets can also be used for the initial episode of genital herpes (1 g bid × 10 days).
- Recurrent episodes of genital herpes can be treated w/acyclovir. A short course (800 mg tid × 2 days) is effective. Other treatment options include 800 mg PO bid × 3-5 days, generally started during the prodrome or within 2 days of onset of lesions; famciclovir is also useful for treatment of recurrent genital herpes (dose is 125 mg q12h × 5 days in pts w/nl renal function) started at the first sign of sx; or valacyclovir (dose is 500 mg q12h × 3 days in pts w/nl renal function).
- Application of topical cool compresses w/Burow’s solution for 15 min 4-6× qd may be soothing in pts w/extensive erosions on the vulva and penis.

**Clinical Pearl**

- >85% of adults have serologic evidence of HSV-1 infection. The seroprevalence of adults wHSV-2 in the United States is 25%; however, only about 20% of these pts recall having sx of HSV infection.

**GIANT CELL ARTERITIS (TEMPORAL ARTERITIS, CRANIAL ARTERITIS)**

**Definition**

Systemic segmental granulomatous inflammation predominantly involving the arteries of the carotid system in pts aged >50 yr. However, it can involve any large or medium-sized arteries.

**Diagnosis**

The presence of any 3 of the following 5 items allows the dx of giant cell arteritis w/a sensitivity of 94% and a specificity of 91%:

- Age at disease onset >50 yr
- New onset or new type of headache
- Temporal artery tenderness or ↓ pulsation on PE
- ESR >50 mm/hr
- Artery bx w/vasculitis and mononuclear cell infiltrate or granulomatous changes

**Treatment**

- Stable pts w/o significant ocular involvement: prednisone 40-60 mg/day in divided doses, continued for a few weeks until sx resolve and ESR returns to nl. If the ESR remains nl, prednisone can be ↓ by 5 mg every other week until a dose of 20 mg/day is reached. Subsequent dose reductions should be by 2.5 mg/day q2-4wk. When the total dose reaches 5 mg/day, reduction should be by 1 mg every 2–4 wk as tolerated. Usual duration of prednisone treatment is 6 mo–2 yr.
- Very ill pts and those w/significant ocular involvement (e.g., visual loss in one eye): IV methylprednisolone 250 mg q6h × 3 days before starting oral prednisone.

**GIARDIASIS**

**Definition**

Intestinal or biliary tract infection caused by the protozoal parasite *Giardia lamblia*.
**Diagnosis**

**H&P**
- Clinical presentation: >70% w/1 or more intestinal sx (diarrhea, flatulence, cramps, bloating, nausea)
- Labs
  - Stool specimen (3 specimens yield 90% sensitivity) or duodenal aspirate for microscopic examination to establish dx and exclude other pathogens
  - Serum alb, vitamin B₁₂ levels, and stool fat test to exclude malabsorption

**Treatment**
- Nitazoxanide 500 mg PO 2× qd for 3 days
- Metronidazole 250 mg PO 3× qd for 7 days (metronidazole avoided in pregnancy) or tinidazole 2 mg PO once
- Paromomycin 25-30 mg/kg/day in 3 doses for 5-10 days

### GI BLEEDING

#### General Approach
- Evaluate the extent (severity) of the bleeding and assess hemodynamic stability.
- Locate the site of the bleeding:
  - Upper GI bleeding (above the ligament of Treitz): PUD (40%-79%), gastritis/duodenitis (5%-30%), esophageal or gastric varices (6%-21%), Mallory-Weiss tears (3%-15%), tumors (2%-3%), AV (<1%) and aortoenteric fistulas (<1%).
  - Lower GI bleeding (below the ligament of Treitz): acute massive lower GI bleeding causes are diverticular disease (17%-40%), angiodysplasia (2%-30% of colonic bleeds, 70%-80% of small bowel bleeds), neoplasm (11%-14%), IBD (9%-21%), ischemic colitis (5%), solitary rectal ulcer (2%-5%), NSAID-induced colonic ulceration (1%), acute infectious colitis (1%), pseudomembranous colitis (1%), post-polypectomy bleeding (2%-5%), radiation colitis (2%-5%), hemorrhoids (1%), and anal fissures (1%).

**Hx**
- Meds (ASA, steroids, “blood thinners,” NSAIDs)
- Prior GI or vascular surgery
- H/o GI dx or bleeding
- Smoking
- Alcohol intake (gastritis, esophageal varices)
- Sx of PUD
- Associated diseases (CAD, diabetes, HTN, hematologic disorders, renal failure)
- Protracted retching and vomiting (consider gastric or gastroesophageal tear [Mallory-Weiss syndrome])
- Weight loss, anorexia (consider carcinoma)
- Color and character of stool (i.e., hematochezia or melena, constipation or diarrhea)
- Presence or absence of hematemesis

**PE**
- VS: tachycardia, hypotension, postural changes (orthostatic hypotension); a pulse ↑>20 bpm or a postural ↓ in systolic BP >10-15 mm Hg indicates blood loss >1 L.
- Pts taking β-adrenergic blockers may not demonstrate significant tachycardia w/volume depletion.
- Cardiorespiratory exam: murmurs (↑ incidence of angiodysplasia in pts w/AS), pulmonary rales, JVD to determine rapidity of volume replacement
- Abd exam:
  - Observe for masses, tenderness, distention, ascites.
  - Auscultate for bowel sounds or Abd bruits.
  - Look for evidence of liver disease (hepatomegaly, splenomegaly, abnl vascular patterns, gynecomastia, spider angiomas, palmar erythema, testicular atrophy).
- DRE: check for masses, strictures, hemorrhoids; test stool for occult blood and inspect it for abnormalities (tarry, blood streaked, bright red, mahogany color).
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Skin: check for jaundice (liver disease), ecchymoses (coagulation abnormality), cutaneous telangiectasia (Rendu-Osler-Weber disease), buccal pigmentation (Peutz-Jeghers syndrome), and other mucocutaneous changes (Ehlers-Danlos syndrome).

Look for evidence of metastatic disease (cachexia, firm nodular liver).

If the pt is not experiencing hematemesis and endoscopy is not immediately available, an NG tube may be placed for gastric lavage while awaiting endoscopy to determine whether the bleeding is emanating from the upper GI tract (presence of bright red blood clots or coffee-ground–like guaiac-positive aspirate); however, the sensitivity and specificity of this process are limited. A negative aspirate does not rule out upper GI bleeding because it could have subsided or the pt could be bleeding from the duodenal bulb w/o reflux into the stomach. Lavage w/500 mL of NS. Failure to clear blood w/gastric lavage indicates persistent bleeding and the need for more urgent endoscopy.

Initial Management

Stabilize the pt: insert two large-bore (18-gauge) IV catheters and administer lactated Ringer’s solution or NS; the rate of volume replacement is based on the estimated blood loss, clinical condition, and h/o CVD, including CHF.

Type and crossmatch for 2-8 U of PRBCs, depending on the estimated blood loss, and transfuse as necessary. Aim for Hct ≥30 for elderly pts w/multiple comorbid conditions and ≥20 for young, healthy individuals.

Initial labs:

- Hgb/Hct
  - Initial value should be considered erroneously ↑ until serum volume is replaced by crystalloid fluid.
  - After bleeding ceases, the Hct may continue to ↓ for up to 6 hr, and full equilibration may require 24 hr. Follow the Hgb/Hct q6-8hr while active bleeding is present and ↓ to daily assessments once bleeding has stopped.
  - The Hct generally ↓ by 2-3 points and the Hgb falls by 1 point for every 500 mL of blood lost.
- BUN: in the absence of renal disease, the BUN level may help determine the severity of the bleeding; a simultaneous Cr level may also be of value because the disparity in the BUN:Cr ratio will reveal the extent of the bleeding more accurately; BUN:Cr >36 is suggestive of UGI bleeding. ↑ BUN levels can be confusing if the bleeding is insidious and might mark prerenal azotemia secondary to the bleed.
- PT, APTT, and platelet count should be calculated to exclude bleeding disorders; other useful initial labs are LFTs, serum electrolytes, and glucose.

- ECG: r/o myocardial ischemia secondary to severe anemia

Endoscopic Evaluation

EGD: indicated when blood or guaiac + coffee-ground–like material is obtained from the NS aspirate or if lower endoscopic findings are negative. It should be performed urgently in hemodynamically unstable pts or those found to still be actively bleeding by NG lavage or in those requiring blood transfusion. Otherwise, it should ideally be performed within 24 hr of the hospital admission. In addition, if a therapeutic procedure (e.g., bipolar heater probe, laser cauterization, injection sclerotherapy, or band ligation) is considered, endoscopy should be done on an emergency basis.

Colonoscopy should be performed initially if lower GI bleeding is suspected within 24 hr of hospital admission after adequate bowel preparation.

Imaging

- Arteriography can identify briskly bleeding sources. Overall diagnostic sensitivity of arteriography is 41%. Mesenteric arteriography is useful to identify bleeding from AV malformations.
- Radionuclide scans may be used before angiography to determine which pts are bleeding sufficiently to make a positive angiographic result more
likely. Bleeding at rates as low as 0.1 mL/min can be detected by such radionuclide scans. A positive “immediate blush” is a good indication for urgent angiography, whereas a negative “delayed blush” is an indication for observation and elective colonoscopy.

- Technetium Tc 99m ($^{99m}$Tc) pertechnetate scan (Meckel scan) selectively tags acid-secreting cells (gastric mucosa); it is used most often for unexplained bleeding in infants and young adults.
- $^{99m}$Tc–sulfur colloid scan is very sensitive in detecting lesions w/low bleeding rates; its major drawbacks are as follows:
  - Short half-life (difficulty in detecting intermittent bleeding)
  - Affinity of the colloid for liver and spleen (colonic bleeding may be missed if it originates in a region superimposed on areas of liver or spleen uptake)
- $^{99m}$Tc-labeled RBC scan: its major advantage over the sulfur colloid scan is its long duration; it is useful for intermittent bleeding because the pt can be monitored for GI bleeding for 24-48 hr. Its disadvantage is that it has a high false-localization rate.

Selective angiography:

- On occasion, this is the first test ordered in actively bleeding pts; but in most situations, it is reserved for massive, ongoing bleeding, especially when endoscopy is not feasible, or when endoscopic evaluation is unrevealing w/recurrent or persistent blood loss.
- Angiography may also be therapeutic because vasoconstrictors, autologous clots, or Gelfoam emboli can be administered intra-arterially at the time of angiography to occlude the bleeding vessel.
- Major drawbacks are the high rate of bleeding (>0.5 mL/min) necessary for dx and the risk of allergic reaction to the contrast dye.
- Advantages include the fact that no bowel preparation is required and anatomic localization is accurate.
- Enhanced helical CT scanning w/IV contrast material is a newer diagnostic modality. Its role remains to be fully defined.

Rx

The treatment of acute GI bleeding may require multiple modalities and is mentioned only briefly.

- Correct bleeding abnormalities by administering FFP or vitamin K if the pt has a coagulopathy and platelets if the pt is severely thrombocytopenic.
- IV PPIs in cases of probable peptic ulcer or gastritis. After endoscopic treatment of bleeding peptic ulcers, IV PPIs ↓ the risk of recurrent bleeding.
- Octreotide: IV bolus of 50-100 µg followed by IV infusion of 25-50 µg/hr for acute variceal bleeding. Another useful agent is terlipressin.

Endoscopy:

- Sclerotherapy or endoscopic variceal ligation for bleeding varices
- Injection Rx (e.g., epinephrine, saline), bipolar electrocoagulation, and heater-probe Rx are equally effective modalities in the treatment of bleeding peptic ulcer.
- Balloon tamponade w/Sengstaken-Blakemore tube or a Minnesota quadruple tube (modification of Sengstaken-Blakemore tube w/a port to suction above the esophageal balloon): indicated for severe bleeding from esophageal varices if octreotide or other endoscopic treatment modalities are ineffective.
- Radiologic modalities: localized infusion of vasopressin, autologous clots, or foreign coagulating substances (e.g., Gelfoam) in the bleeding vessel during or after arteriography.
- Surgery: indicated at the onset of dx of aortoduodenal fistula, but it is not suggested as the initial Rx in cases of other causes of GI bleeding until a definitive dx is made and other noninvasive modalities are tried. Surgical approach may be necessary in the following situations:
  - Rebleeding in a hospitalized pt
  - Bleeding episode that requires transfusion of >4 U of PRBCs in 24 hr or >10 U of PRBCs in total
  - Endoscopic visualization of a “naked” vessel in a peptic ulcer unresponsive to injection or coagulation Rx
GLOMERULONEPHRITIS, ACUTE

Definition
Immunologically mediated inflammation primarily involving the glomerulus that can result in damage to the basement membrane, mesangium, or capillary endothelium.

Diagnosis

**Labs**
- U/A (hematuria [dysmorphic erythrocytes and red cell casts], proteinuria)
- Serum Cr (to estimate GFR), BUN
- 24-hr urine for protein excretion and CrCl (to document degree of renal dysfunction and amount of proteinuria). Proteinuria in AGN typically ranges from 500 mg/day to 3 g/day, but nephrotic-range proteinuria (>3.5 g/day) may be present.
- Streptococcal tests (Streptozyme), antistreptolysin O (ASO) quantitative titer (highest in 3-5 wk); ASO titer, however, is not related to severity of renal disease, duration, or prognosis.
- Additional useful tests, depending on the hx: anti-DNA Abs (r/o SLE), CH50 level (if elevated, obtain C3, C4 levels), TGs, cryoglobulins, hepatitis B and C serologies, ANCA, cANCA (in suspected cases of Wegener’s granulomatosis), pANCA found in pauci-immune (lack of immune deposits) idiopathic RPGN w/ or w/o systemic vasculitis, anti–glomerular basement membrane (type alpha3 IV collagen) Abs
- Hct (↓ in GN), platelet count (thrombocytopenia in cases of lupus nephritis)
- Anti-GBM Ab (in Goodpasture’s syndrome)
- Blood cultures are indicated in all febrile pts.
- Renal bx and light, electron, and immunofluorescent microscopy can confirm dx. Kidney bx generally reveals a granular pattern in post-streptococcal GN, linear pattern in Goodpasture’s syndrome; absence of immune deposits suggests vasculitis.
- Immunofluorescence: generally reveals C3; negative immunofluorescence suggests Wegener’s granulomatosis, idiopathic crescentic GN, or polyarteritis nodosa.

**Imaging**
- CXR: r/o pulmonary congestion, Wegener’s granulomatosis, and Goodpasture’s syndrome
- Renal U/S: evaluate renal size and determine extent of fibrosis. A kidney size of <9 cm is suggestive of extensive scarring and low likelihood of reversibility.
- Echo: in pts w/new cardiac murmurs or + blood cultures to r/o endocarditis and pericardial effusion
- Angiography or bx of other affected organs if systemic vasculitis is suspected

Etiology (Table 3-18)
AGN may be due to primary renal disease or a systemic disease. A number of pathogenic processes (e.g., Ab deposition, cell-mediated immune mechanisms, complement activation, hemodynamic alterations) have been implicated in the pathogenesis of glomerular inflammation. Medical disorders generally associated w/GN are the following:
- Post–group A beta-hemolytic streptococcus infection (other infectious etiologies, including endocarditis and visceral abscess)
- Collagen-vascular diseases (SLE)
- Vasculitis (Wegener’s granulomatosis, polyarteritis nodosa)
- Idiopathic GN (membranoproliferative, idiopathic, crescentic, IgA nephropathy)
- Goodpasture’s syndrome
- Other cryoglobulinemia (Henoch-Schönlein purpura)
- Drug induced (gold, penicillamine)

Treatment
- Avoidance of salt if edema or HTN is present
- ↓ Protein intake (approximately 0.5 g/kg/day) in pts w/renal failure
- Fluid restriction in pts w/significant edema
### Summary of Primary Renal Diseases That Present as Acute Glomerulonephritis

<table>
<thead>
<tr>
<th>Diseases</th>
<th>PSGN</th>
<th>IgA Nephropathy</th>
<th>Membranoproliferative GN</th>
<th>Idiopathic RPGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical manifestations</td>
<td>90%</td>
<td>50%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>Age and sex</td>
<td>All ages; mean, 7 yr; 2:1 male</td>
<td>15-35 yr; 2:1 male</td>
<td>15-30 yr; 6:1 male</td>
<td>Mean, 58 yr; 2:1 male</td>
</tr>
<tr>
<td>Acute nephritis syndrome</td>
<td>Occasionally</td>
<td>50%</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Asymptomatic hematuria</td>
<td>10%-20%</td>
<td>Rare</td>
<td>Rare</td>
<td>10%-20%</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>70%</td>
<td>30%-50%</td>
<td>Rare</td>
<td>25%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50% (transient)</td>
<td>Very rare</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Latent period of 1-3 wk</td>
<td>Follows viral syndromes</td>
<td>Pulmonary hemorrhage; iron deficiency anemia</td>
<td>None</td>
</tr>
</tbody>
</table>

**Other**

<table>
<thead>
<tr>
<th>Laboratory findings</th>
<th>↑ ASO titers (70%)</th>
<th>↑ Serum IgA (50%)</th>
<th>Positive anti-GBM antibody</th>
<th>Positive ANCA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive streptolysin (95%)</td>
<td>IgA in dermal capillaries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenetics</td>
<td>HLA-B12, D “EN” (9)*</td>
<td>HLA-Bw 35, DR4 (4)*</td>
<td>HLA-DR2 (16)*</td>
<td>None established</td>
</tr>
</tbody>
</table>

**Renal disease**

<table>
<thead>
<tr>
<th>Light microscopy</th>
<th>Diffuse proliferation</th>
<th>Focal proliferation</th>
<th>Focal → diffuse proliferation with crescents</th>
<th>Crescentic GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunofluorescence</td>
<td>Granular IgG, C3</td>
<td>Diffuse mesangial IgA</td>
<td>Linear IgG, C5</td>
<td>No immune deposits</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td>Subepithelial humps</td>
<td>Mesangial deposits</td>
<td>No deposits</td>
<td>No deposits</td>
</tr>
<tr>
<td>Prognosis</td>
<td>95% resolve spontaneously</td>
<td>5% RPGN or slowly progressive</td>
<td>Slow progression in 25%-50%</td>
<td>75% stabilize or improve if treated early</td>
</tr>
<tr>
<td>Treatment</td>
<td>Supportive</td>
<td>None established</td>
<td>Plasma exchange, steroids, cyclophosphamide</td>
<td>Steroid pulse therapy</td>
</tr>
</tbody>
</table>

*Relative risk.

ANCA, antineutrophil cytoplasmic antibody; ASO, antistreptolysin O; GBM, glomerular basement membrane; HLA, human leukocyte antigen; PSGN, post-streptococcal glomerulonephritis; RPGN, rapidly progressive glomerulonephritis.
Diseases

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Avoidance of ↑ potassium foods
Correction of electrolyte abnormalities (hypocalcemia, hyperkalemia) and acidosis (if present)
Rx of streptococcal infection w/PCN (or erythromycin in PCN-allergic pts)
Furosemide in pts w/significant HTN or edema; hydralazine or nifedipine in pts w/HTN
Immunosuppressive treatment in pts w/heavy proteinuria or rapidly ↓ GFR (high-dose steroids, cyclosporine, cyclophosphamide); corticosteroids generally not useful in post-streptococcal GN
Fish oil (n-3 fatty acids) 12 g/day: may prevent or slow down loss of renal function in pts w/IGA nephropathy
Plasma exchange Rx and immunosuppressive drugs (prednisone and cyclophosphamide): effective in Goodpasture’s syndrome
Short-term Rx w/IV cyclophosphamide followed by maintenance Rx w/mycophenolate mofetil or azathioprine is more efficacious and safer than long-term Rx w/IV cyclophosphamide in pts w/proliferative lupus nephritis.

Clinical Pearl
Prognosis is generally related to histology, w/excellent prognosis in pts w/min. change GN and focal segmental proliferative GN; 25%-30% of pts w/mesangial IgA disease and membranous GN generally progress to chronic renal failure; >70% of pts w/ mesangial capillary GN will develop chronic renal failure.

174 GONORRHEA

Diagnosis

H&P
Males: purulent d/c from anterior urethra w/dysuria appearing 2–7 days after infecting exposure. May have rectal infection causing pruritus, tenesmus, and d/c or may be asymptomatic.
Females: initial urethritis, cervicitis may occur a few days after exposure, frequently mild. In about 20% of cases, uterine invasion occurs after menstrual period w/signs and sx of endometritis, salpingitis, or pelvic peritonitis. The pt may have purulent d/c, inflamed Skene’s or Bartholin’s glands.
Classic presentation of acute gonococcal PID is fever, abd and adnexal tenderness, cervical motion tenderness, often absence of purulent d/c. PE may be nl if asymptomatic.

Labs
Gonorrhea culture on Thayer–Martin medium (Organism is fastidious, requires aerobic conditions w/↑ CO₂ atmosphere. Incubate ASAP.)
Serologic testing for syphilis on all pts
Chlamydia testing on all pts
Offer of HIV counseling and testing

Treatment

Uncomplicated Infections of the Cervix, Urethra, and Rectum
Cefixime 400 mg PO × 1 dose or
Ceftriaxone 125 mg IM × 1 dose or
Doxycycline 100 mg PO bid × 7 days
Dual Rx w/azithromycin and doxycycline may prevent the development of antimicrobial-resistant N. gonorrhoeae and will cover co-infection w/C. trachomatis.
Alternatives:
• Cefpodoxime 400 mg single dose or
• Cefuroxime 1 g PO single dose

Uncomplicated Pharyngeal Infection
Ceftriaxone 125 mg IM × 1 dose

Clinical Pearls
Pregnant pts require test of cure (as do those treated w/regimens other than ceftriaxone/doxycycline); reculture 4–7 days after treatment.
Treatment failure in nonpregnant pts is rare, and test of cure is not required. Rescreening in 1-2 mo detects treatment failures and reinfections.

Sexual partners should all be identified, examined, and cultured and receive presumptive treatment.

175 GOODPASTURE’S SYNDROME

Definition
Triad of GN, pulmonary hemorrhage, and Ab to basement membrane antigens.

Diagnosis
H&P
- Clinical presentation: dyspnea, cough, hemoptysis, skin pallor, fever, arthralgias (may be mild or absent at the time of initial presentation)

Labs
- U/A: microscopic hematuria and proteinuria
- Presence of circulating serum anti-GBM Ab
- Absence of circulating immunocomplexes, antineutrophils, cytoplasmic Ab, and cryoglobulins
- ↑ BUN and Cr from RPGN
- Immunofluorescence studies of renal bx material: linear deposits of anti-GBM Ab, often accompanied by C3 deposition
- Anemia from iron deficiency (secondary to blood loss and iron sequestration in the lungs)

Imaging
- CXR: fluffy alveolar infiltrates, evidence of pulmonary hemorrhage

Etiology
- Presence of GBM Ab deposition in kidneys and lungs w/subsequent pulmonary hemorrhage and GN

Treatment
- Plasma exchange Rx
- Immunosuppressive Rx w/prednisone (1 mg/kg/day) and cyclophosphamide (2 mg/kg/day)
- Dialysis support in pts w/renal failure

Clinical Pearl
- Goodpasture’s syndrome accounts for 5% of all cases of RPGN.

176 GOUT

Definition
Disease characterized by deposition of monosodium urate crystals in and about joints, w/subsequent acute or chronic arthritis.

Diagnosis
H&P
- The typical presentation is monarticular and characterized by sudden severe pain involving the first metatarsophalangeal joint (podagra), although the midtarsal and ankle are also frequently affected; any joint may be involved, but acute polyarthritis is uncommon.
- PE reveals a warm, tender, swollen, erythematous joint; fever may be present, particularly if several joints are involved. Extensive soft tissue swelling, heat, and erythema extending to above and below the affected joint are frequently present and may be confused w/cellulitis.

Labs
- Serum uric acid level may be ↑, but it is often nl during the acute attack, later rising when the sx resolve.
- Aspiration and analysis of synovial fluid from the inflamed joint confirm the dx; examination of the fluid w/a polarized light microscope w/compensator reveals monosodium urate crystals (needle-shaped, strongly negative birefringent crystals) w/synovial fluid leukocytes.
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**Treatment**
- NSAIDs: indomethacin, 50 mg q8h for 3-4 days, then gradually tapered off during approximately 1-2 wk (depending on the pt’s clinical response); naproxen, sulindac, and other NSAIDs are also effective; ketorolac (60 mg) may be given IM in NPO pts.
- Colchicine can be given PO or IV; PO dose is 1.2 mg followed by a second dose of 0.6 mg one hour later. IV administration has been associated w/↑ risk of bone marrow suppression and renal or hepatic cell damage. Extravasation can also cause tissue necrosis.
- Glucocorticoids (triamcinolone acetonide or ACTH): generally reserved for pts w/contraindications to NSAIDs or colchicine or if oral medication is precluded (e.g., postoperatively). Triamcinolone acetonide, 60 mg IM; or ACTH, 40IM or 25 by slow IV infusion. Intra-articular steroids may be used to treat a single inflamed joint (dexamethasone phosphate 1-6 mg).
- Prednisone 20-40 mg PO qd can be used short term in pts refractory or intolerant to NSAIDs/colchicine or responding poorly to these agents.

**Clinical Pearls**
- Uricosuric agents (e.g., probenecid) or xanthine oxidase inhibitors (allopurinol, febuxostat) are used in pts w/frequent recurrent attacks. Hypouricemic Rx should not be started for at least 2 wk after the acute attack has resolved because it may prolong the acute attack and can also precipitate new attacks by rapidly lowering the serum uric acid level.
- Colchicine, 0.6 mg PO bid, is indicated for acute gout prophylaxis before hypouricemic Rx is started. It is generally discontinued 6-8 wk after normalization of serum urate levels. Long-term colchicine Rx (0.6 mg qd or bid) may be necessary in pts w/frequent gout attacks despite the use of uricosuric agents. It can also be used as an alternative to uricosuric agents.

**GRAVES’ DISEASE**

**Definition**
Hypermetabolic state characterized by thyrotoxicosis, diffuse goiter, and infiltrative ophthalmopathy.

**Diagnosis**

**H&P**
- Tachycardia, palpitations, tremor, hyperreflexia
- Goiter, exophthalmos (50% of pts), lid retraction, lid lag
- Nervousness, weight loss, heat intolerance, AF
- ↑ Sweating, brittle nails, clubbing of fingers
- Localized dermopathy (1%-2% of pts) is most frequent over the anterolateral aspects of the shins but can be found at other sites (especially after trauma).
- Men may have gynecomastia, ↓ libido, and erectile dysfunction. Women often have irregular menses.

**Labs**
- ↑ Free thyroxine (T₄) and free triiodothyronine (T₃)
- ↓ TSH
- Presence of thyroid-stimulating immunoglobulin or thyrotropin-receptor Abs (useful in selected pts to differentiate Graves’ disease from toxic nodular goiter)
- 24-hr RAI uptake (RAIU): ↑ homogeneous uptake
- CT or MRI of the orbits is useful if there is uncertainty about the cause of ophthalmopathy.

**Etiology**
- Due to circulating IgG Abs that bind to and activate the G protein–coupled thyrotropin receptor. This activation stimulates follicular hypertrophy and hyperplasia, causing thyroid enlargement as well as ↑ in thyroid hormone production.

**Treatment**
- Antithyroid drugs (ATDs) to inhibit thyroid hormone synthesis or peripheral conversion of T₄ to T₃: methimazole or propylthiouracil
Diseases
- *Ascending flaccid polyradiculopathy* is the inflammatory cause most commonly affecting motor function. GBS is the most common cause of acute ascending flaccid paralysis.

**Clinical Pearls**
- Elderly pts can have an atypical presentation of Graves’ disease (apathetic hyperparathyroidism).
- Smoking is associated w/↑ risk of progression of Graves’ ophthalmopathy.

**178 GUILLEIN-BARRÉ SYNDROME (GBS)**

**Definition**
Acute inflammatory demyelinating polyradiculopathy predominantly affecting motor function. GBS is the most common cause of acute ascending flaccid paralysis.

**Diagnosis**

**Hx**
- Rapid progression of acute symmetric progressive weakness, usually > distally than proximally and > in the legs than in the arms.
- The pt often reports difficulty in ambulating, getting up from a chair, or climbing stairs.
- The ascending paralysis affects motor nerves more than sensory nerves.
  - Sensory loss (predominantly position and vibration senses) is variable but usually mild.
- In some pts, the initial manifestations may involve the cranial musculature or the UEs (e.g., tingling of the hands).
- As a general rule, weakness reaches its max within 14 days.

**PE**
- Symmetric weakness, initially involving proximal muscles, subsequently both proximal and distal muscles.
- ↓ or absent reflexes bilaterally early in the disease.
- Minimum to moderate glove and stocking anesthesia.
- Ataxia and pain in a segmental distribution may occur in some pts (caused by involvement of posterior nerve roots).
- Autonomic abnormalities (bradycardia or tachycardia, hypotension or HTN) may also occur.
- Respiratory insufficiency (caused by weakness of intercostal muscles).
- Facial paresis, difficulty swallowing (secondary to cranial nerve involvement).

** Labs **
- CBC may reveal early leukocytosis w/left shift. Electrolytes to exclude metabolic causes of weakness.
- Heavy metal testing, urine porphyria screen, CK, HIV titers, and neuroimaging of the brain and spinal cord if dx uncertain. Nerve root enhancement may be seen on MRI of the LS spine.
- Ab against ganglioside GO_{1a} may be present in up to 90% of pts w/Miller-Fisher syndrome. IgG Ab against ganglioside GM_{1} may be associated w/acute motor axonal neuropathy. There are no antiganglioside Abs commonly associated w/acute inflammatory demyelinating polyneuropathy.
In equivocal cases (especially if peripheral nerve vasculitis is a concern), nerve bx may aid in confirming a dx of GBS. Sensory nerve bx demonstrates segmental demyelination w/infiltration of monocytes and T cells into the endoneurium. Axonal loss is commonly seen in sensory nerve bx specimens in GBS.

LP: typical findings include ↑ CSF protein (especially IgG) and presence of few mononuclear leukocytes (albuminocytologic dissociation).

**EMG/NCS**

- Slowed conduction velocities; ↑ motor, sensory, and F wave latencies. EMG may be normal in first 7-10 days.

**Etiology**

- ½ of all pts give a h/o respiratory or GI illness (e.g., *Campylobacter jejuni*) within 30 days of onset of neurologic sx.

**Treatment**

- Close monitoring of respiratory function (frequent [q1h initially] bedside measurements of FVC and negative inspiratory force to assess pulmonary muscle strength) because respiratory failure is the major potential problem in GBS.

- Infusion of IV immune globulin (IVIG 0.4 g/kg/day for 5 days). Always check serum IgA levels before infusion to prevent anaphylaxis in deficient pts.

- Plasma exchange: 200-250 mL/kg during five sessions qod

- IVIG and plasma exchange are equally effective. The selection of one or the other is determined by availability and risk of particular complications. For example, plasma exchange should be avoided in pts w/prominent autonomic dysfunction.

- There is no proven benefit of combining IVIG and plasma exchange.

- Mechanical ventilation may be needed if FVC is <12-15 mL/kg, VC is rapidly ↓ or is <1000 mL, negative inspiratory force is <-20 cm H2O, Pao2 is <70, or the pt is having significant difficulty clearing secretions or is aspirating.

- Ventilatory support may be necessary in 10%-20% of pts. Adequate fluid/electrolyte support and nutrition are necessary, especially in pts w/dysautonomia or bulbar dysfunction.

- Aggressive nursing care is required to prevent decubiti, infections, fecal impactions, and pressure nerve palsies and for mouth care to prevent ventilator-associated pneumonias.

- Monitor and treat autonomic dysfunction (bradyarrhythmias or tachyarrhythmias, orthostatic hypotension, systemic HTN, altered sweating).

- Treat back pain and dysesthesia w/low-dose tricyclics, gabapentin, and the like. Opiate narcotics can be used cautiously in the short term but may compound dysautonomia.

- Stress ulcer prevention in pts receiving ventilator support

- Discuss physical and occupational Rx rehabilitation, including supportive devices.

**HEART BLOCK, SECOND DEGREE**

**Definition**

Blockage of some (but not all) impulses from the atria to the ventricles. There are two types of second-degree AV block:

- Mobitz type I (Wenckebach) (Fig. 3-20):

**FIGURE 3-20.** Mobitz I second-degree atrioventricular block (Wenckebach).
• There is a progressive prolongation of the PR interval before an impulse is completely blocked; the cycle repeats periodically.
• Cycle w/dropped beat is <2 times the previous cycle.
• Site of block is usually AV node (proximal to the bundle of His).

Mobitz type II (Fig. 3-21):
• There is a sudden interruption of AV conduction w/o prior prolongation of the PR interval.
• Site of block is infranodal.

![Figure 3-21. Mobitz II second-degree atrioventricular block. Notice that every alternate P wave is blocked.](image)

**Etiology**

*Mobitz Type I*
- Vagal stimulation
- Degenerative changes in the AV conduction system
- Ischemia at the AV nodes (particularly in inferior wall MI)
- Drugs (digitalis, quinidine, procainamide, adenosine, CCBs, β-blockers)
- Cardiomyopathies
- AI
- Lyme carditis

*Mobitz Type II*
- Degenerative changes in the His-Purkinje system
- Acute anterior wall MI
- Calcific AS

**Treatment**

*Mobitz Type I*
- Treatment generally is not necessary. This type of block is usually transient.
- If symptomatic (e.g., dizziness), atropine 1 mg (may repeat once after 5 min) may be tried to ↑ AV conduction; if no response, insert temporary pacemaker.
- If block is secondary to drugs (e.g., digitalis), discontinue the drug.
- If associated w/anterior wall MI and wide QRS escape rhythm, consider insertion of temporary pacemaker.
- Significant AV block post-MI may be caused by adenosine produced by the ischemic myocardium. These arrhythmias (which may be resistant to conventional Rx such as atropine) may respond to theophylline (adenosine antagonist).

*Mobitz Type II*
- Pacemaker insertion is needed because this type of block is usually permanent and often progresses to complete AV block.

**180| HEART BLOCK, THIRD DEGREE**

**Definition**
Complete blockage of all AV conduction. The atria and ventricles have separate, independent rhythms.

**Diagnosis**

*H&P*
- Pts may present w/dizziness, palpitations, Stokes-Adams syncopal attacks, CHF, angina.
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HEAT STROKE

**Definition**
A life-threatening heat illness characterized by extreme hyperthermia, dehydration, and neurologic manifestations (core temperature >40°C).

**Diagnosis**
**H&P**
- Neurologic manifestations (seizures, tremor, hemiplegia, coma, psychosis, and other bizarre behavior)
- Evidence of dehydration (poor skin turgor, sunken eyeballs)
- Tachycardia, hyperventilation
- Skin is hot, red, and flushed.
- Sweating is often (not always) absent, particularly in elderly pts.

**Labs**
- ↑ BUN, Cr, Hct
- Hyponatremia or hypernatremia, hyperkalemia or hypokalemia
- ↑ LDH, AST, ALT, CPK, bili
- Lactic acidosis, respiratory alkalosis (secondary to hyperventilation)
- Myoglobinuria, hypofibrinogenemia, fibrinolysis, hypocalcemia

**Treatment**
- Remove the pt’s clothes and place the pt in a cool and well-ventilated room.
- If unconscious, position pt on his/her side and clear the airway. Protect airway and augment oxygenation (e.g., nasal O₂ at 4 L/min to keep oxygen saturation >90%).
- Monitor body temperature q5min. Measurement of the pt’s core temperature w/rectal probe is recommended. The goal is to ↓ the body temperature to 39°C (102.2°F) in 30-60 min.

**ECG** (Fig. 3-22)
- P waves constantly change their relationship to the QRS complexes.
- Ventricular rate is usually <50 bpm (may be higher in congenital forms).
- Ventricular rate is generally lower than the atrial rate.
- QRS complex is wide.

**Etiology**
- Degenerative changes in His-Purkinje system
- Acute anterior wall MI
- Calcific AS
- Cardiomyopathy
- Trauma
- CV surgery
- Congenital

**Treatment**
- Immediate pacemaker insertion unless the pt has congenital third-degree AV block and is completely asymptomatic

Figure 3-22. Third-degree atrioventricular block. Strips A and B taken several hours apart. A, Atrial rate of 75 bpm. Ventricles are beating independently at a slow rate of approximately 40 bpm. B, A few hours later, same patient; variations in the shape of QRS complex from beat to beat.
Spray the pt w/cool mist and use fans to enhance airflow over the body (rapid evaporation method).

Immerse of the pt in ice water, stomach lavage w/iced saline solution, IV administration of cooled fluids, and inhalation of cold air are advisable only when the means for rapid evaporation are not available. Immersion in tepid water (15°C [59°F]) is preferred to ice water immersion to minimize risk of shivering.

Use of ice packs on axillae, neck, and groin is controversial because they ↑ peripheral vasoconstriction and may induce shivering.

Antipyretics are ineffective because the hypothalamic set point during heat stroke is nl despite the ↑ body temperature.

Intubate a comatose pt, insert a Foley catheter, and start nasal O₂. Continuous ECG monitoring is recommended.

Insert at least 2 large-bore IV lines and begin IV hydration w/NS or lactated Ringer’s solution.

Treat complications as follows:
- Hypotension: vigorous hydration w/NS or lactated Ringer’s solution
- Convulsions: diazepam 5-10 mg IV (slowly)
- Shivering: chlorpromazine 10-50 mg IV
- Acidosis: use bicarbonate judiciously (only in severe acidosis)

Observe for evidence of rhabdo, hepatic, renal, or cardiac failure and treat accordingly.

182 HELLP SYNDROME

Definition
The HELLP syndrome is a serious variant of preeclampsia. HELLP is an acronym for Hemolysis, Elevated Liver enzymes, and Low Platelet count. It is the most frequently encountered microangiopathy of pregnancy. There are 3 classes of the syndrome based on the degree of maternal thrombocytopenia as a primary indicator of disease severity:

- Class 1: platelets 50,000/mm³
- Class 2: platelets >50,000/mm³ to 100,000/mm³
- Class 3: platelets >100,000/mm³

Diagnosis

H&P
Although many women w/HELLP syndrome will be asymptomatic, 80% report RUQ pain and 50%-60% present w/excessive weight gain and worsening edema.

Labs

Initial assessment of suspected HELLP syndrome should include a CBC, U/A, serum Cr, LDH, uric acid, indirect and total bilirubin levels, and AST/ALT.

Tests of PT, APTT, fibrinogen, and fibrin split products are reserved for those women w/platelet count well below 100,000/mm³.

Definitive lab criteria remain to be validated prospectively. Most commonly used criteria include hemolysis defined by the presence of an abnl peripheral smear w/schistocytes, ↑ LDH >600 U/L, and total bilirubin >1.2 mg/dL; ↑ AST >70 U/L and LDH >600 U/L; ↓ platelet count <100,000/mm³.

Treatment

Treatment is dependent on gestational age of the fetus, severity of HELLP, and maternal status. Stabilization of the mother is the first priority.

Assess gestational age thoroughly. Fetal status should be monitored w/nonstress tests, contraction stress tests, and biophysical profile.

Maternal status should be evaluated by H&P and labs.

Mg sulfate is administered for seizure prophylaxis regardless of BP.

BP control: hydralazine or labetalol

In those pregnancies 34 wk or class 1 HELLP syndrome, delivery, either vaginal or abd, within 24 hr is the goal.

In the preterm fetus: corticosteroid Rx to enhance fetal lung maturation

Some reports have shown temporary amelioration of HELLP severity w/administration of high dose of steroids.
Judicious use of blood products, especially in those requiring surgery
Intensive observation for 48 hr post partum; laboratory levels should begin to improve during this time.

183 HEMOCHROMATOSIS

Definition
Autosomal recessive disorder characterized by ↑ accumulation of iron in various organs (adrenals, liver, pancreas, heart, testes, kidneys, pituitary) and eventual dysfunction of these organs if not treated appropriately.

Diagnosis
H&Ps
- ↑ Skin pigmentation
- Hepatomegaly, splenomegaly, hepatic tenderness, testicular atrophy
- Loss of body hair, peripheral edema, gynecomastia, ascites
- Amenorrhea (25% of women)
- Loss of libido (50% of men)
- Arthropathy
- Joint pain (44%)
- Fatigue (45%)

Labs
- Transferrin saturation is best screening test. Values >45% are an indication for further testing; values >52% in men and >50% in women are suggestive of hemochromatosis. Plasma ferritin is also a good indicator of total body iron stores but may be ↑ in many other conditions (inflammation, malignant disease).
- ↑ AST, ALT, alk phos
- Hyperglycemia
- Endocrine abnormalities (↓ testosterone, LH, FSH)
- Measurement of hepatic iron index (hepatic iron concentration divided by age) in liver bx specimen can confirm dx.
- Genetic testing (HFE genotyping for the C282Y and H63D mutations) may be useful in selected pts w/liver disease and suspected iron overload (e.g., pts w/transferrin saturation >40%). Genetic testing should not be performed as part of initial routine evaluation for hereditary hemochromatosis. Once a pt has been identified, first-degree relatives of the index pt should also be screened. The HFE gene test is a PCR-based test usually performed on whole blood sample.

Imaging
- CT or MRI of the liver: useful to exclude other causes and may in some cases show iron overload in the liver

Etiology
- Autosomal recessive disease linked to the region of the short arm of chromosome 6 encoding HLA-A*3; the gene HFE, which contains two missense mutations (C282Y and H63D), has been identified.

Treatment
- Weekly phlebotomies of 1-2 units of blood (each containing approximately 250 mg of iron) should be continued until depletion of iron stores is achieved (ferritin level <50 ng/mL and transferrin saturation <50%). Subsequent phlebotomies can be performed on a PRN basis to maintain a transferrin saturation <50% and a ferritin level <100 ng/mL.
- Deferoxamine (iron chelating agent) is generally reserved for pts w/severe hemochromatosis w/diffuse organ involvement (e.g., liver disease, heart disease) and when phlebotomy is not possible. It is administered in a dose of 0.5-1 g IM qd or 20 mg SC during a 12- to 24-hr period w/constant infusion pump.

184 HEMOLYTIC-UREMIC SYNDROME (HUS)

Definition
Syndrome characterized by nonimmune hemolytic anemia, thrombocytopenia, and severe renal failure.
**Diagnosis**

**H&P**
- Usually preceded by diarrhea (90% of cases)
- Bloody diarrhea (75%)
- Abd pain
- Vomiting
- Fever
- Irritability, lethargy, and seizures (10%)
- HTN
- Pallor
- Anuria or oliguria

**Labs**
- CBC: Hgb <10 g/dL
- Peripheral smear shows the hallmark microangiopathic hemolytic anemia w/schistocytes, burr cells, and helmet cells.
- Thrombocytopenia (platelet counts usually <<60,000/mm³)
- ↑ Reticulocyte count
- ↑ LDH
- ↓ Haptoglobin
- ↑ Indirect bili
- ↑ BUN and Cr
- U/A: proteinuria, microscopic hematuria, and pyuria
- Stool cultures for *E. coli* O157:H7 + in >90% of cases if obtained during the first wk of illness.

**Etiology**
- In children:
  - *E. coli* serotype O157:H7 is the leading cause of HUS.
  - The infection is acquired by eating undercooked red meat, especially hamburgers.
- Other causes of HUS in children and adults are
  - Drugs (cyclosporine, mitomycin, tacrolimus, ticlopidine, clopidogrel, cisplatin, quinine, PCN, penicillamine, oral contraceptives, and quinine used to treat muscle cramps)
  - Infection (*Salmonella, Shigella, Yersinia, group A streptococci, Clostridium difficile, Campylobacter, coxsackievirus, rubella, influenza virus, EBV*)
  - Toxins
  - Pregnancy (usually post partum) and oral contraceptives
  - HIV-associated thrombotic microangiopathy
  - Pneumococcal infection
  - Persons w/relative deficiency in vWF cleaving protease are predisposed to nonenteric infection forms of HUS.

**Treatment**
- BP control
- Blood transfusions for severe anemia; plasma exchange or infusion started within 24 hours after diagnosis
- Abx should be avoided and are not indicated for the treatment of *E. coli* O157:H7.
- Correction of electrolyte abnormalities
- FFP may benefit pts w/nonenteric forms of HUS if they are deficient in VMF-CP (vWF cleaving protease).

**Clinical Pearls**
- Children testing positive for the *E. coli* O157:H7 serotype should not return to school or daycare facilities until two consecutive stools test negative for the microorganism.
- *E. coli* O157:H7 can be transmitted from person to person; therefore, universal precautions and hand washing are recommended in preventing the spread of the infection.
- Adults presenting w/HUS have a worse prognosis than children do.
HEMOPHILIA

Definition
Hereditary bleeding disorder caused by low factor VIII coagulant activity (hemophilia A) or low levels of factor IX coagulant activity (hemophilia B).

Diagnosis

- ↑ PTT
- ↓ Factor VIII: C level distinguishes hemophilia A from other causes of ↑ PTT
- NI factor VIII antigen, PT, fibrinogen level, and bleeding time
- ↓ Factor IX coagulant activity levels in pts w/hemophilia B
- Coagulation factor activity measurement is useful to correlate w/disease severity: NI range is 50-150 U/dL; 5-20 U/dL indicates mild disease, 2-5 U/dL indicates moderate disease, and <2 U/dL indicates severe disease w/spontaneous bleeding episodes.

Etiology

- Hemophilia A: ↓ factor VIII coagulant (VIII:C) activity; can be classified as mild if factor VIII:C levels are >5%; moderate: levels are 1%-5%; severe: levels are <1%.
- Hemophilia B: ↓ factor IX coagulant activity
- Both disorders are congenital.
- Spontaneous acquisition of factor VIII inhibitors (acquired hemophilia) is rare.

Treatment

**Hemophilia A**

- Reversal and prevention of acute bleeding in hemophilia A and B are based on adequate replacement of deficient or missing factor protein.
- The choice of the product for replacement Rx is guided by availability, capacity, concerns, and cost. Recombinant factors cost 2-3 times as much as plasma-derived factors do, and the limited capacity to produce recombinant factors often results in periods of shortage. In the U.S., 60% of pts w/severe hemophilia use recombinant products.
- Factor VIII concentrates are effective in controlling spontaneous and traumatic hemorrhage in severe hemophilia. Recombinant factor VIII is stable w/o added human serum alb (↓ risk of transmission of infectious agents).
- Recombinant activated factor VII is useful to stop spontaneous hemorrhages and to prevent excessive bleeding during surgery in 75% of pts w/inhibitors. Recommended dose is 90 µg/kg of BW q2-3h for treatment of life-threatening hemorrhage.
- Desmopressin acetate 0.3 µg/kg q24h (causes release of factor VIII:C) may be used in preparation for minor surgical procedures in mild hemophiliacs.
- Aminocaproic acid (EACA, Amicar) 4 g PO q4h can be given for persistent bleeding that is unresponsive to factor VIII concentrate or desmopressin.

**Hemophilia B**

- Infuse factor IX concentrates. Factor IX concentrates contain other proteins that may ↑ the risk of thrombosis w/recurrent use. Therefore, factor IX concentrates must be used only when clearly indicated.
- Daily administration of oral cyclophosphamide and prednisone w/o empiric factor VIII Rx is an effective and well-tolerated treatment of acquired hemophilia.

Clinical Pearls

- Despite the advent of virally safe blood products and blood treatment programs, nearly 70% of hemophiliacs are HIV seropositive. Survival is of NI expectancy in HIV-negative pts w/mild disease.
- Intracranial bleeds are the second most common cause of death in hemophiliacs after AIDS. They are fatal in 50% of pts, occur in 10% of pts, and are generally secondary to trauma.
**186 HENOCCH-SCHÖNLEIN PURPURA (HSP)**

**Definition**
Systemic small-vessel vasculitis characterized by palpable purpura in dependent areas (buttocks, legs), GI bleeding and other sx, arthralgias, arthritis, and renal involvement.

**Diagnosis**
- Dx is made on clinical grounds. Skin manifestations are most common. Palpable purpura is seen in 70% of adult pts and is less pronounced in children, in whom GI complaints are more common. Skin bx will show leukocytoclastic vasculitis.
- The presence of 2 of the following 4 American College of Rheumatology criteria yields a diagnostic sensitivity of 87.1% and specificity of 87.7%:
  - Palpable purpura unrelated to thrombocytopenia
  - Age <20 yr at onset of first sx
  - Bowel angina or ischemia
  - Granulocytic infiltration of arteriole or venule walls on bx
- Renal involvement is seen in up to 80% of older children, usually within the first month of illness; <5% of cases progress to ESRD.
- Labs are not specific for HSP. Leukocytosis and eosinophilia may be seen. IgA levels are ↑ in approximately 50% of pts. GN may be present and result in microscopic hematuria, proteinuria, and RBC casts.

**Etiology**
- Presumptive etiology is exposure to a trigger antigen that causes Ab formation.
- Antigen-Ab (immune) complex deposition then occurs in arteriole and capillary walls of skin, renal mesangium, and GI tract. IgA deposition is most common.
- Antigen triggers postulated include drugs, foods, immunization, and upper respiratory and other viral illnesses. Group A strep infection is the most common precipitant in children, seen in up to ½ of cases.
- Serologic and pathologic evidence suggests an association between parvovirus B19 and HSP, which may explain observed cases of HSP that do not respond to corticosteroids or other immunosuppressive Rx.
- Case reports describing development of HSP after treatment w/immunosuppressive agents such as etanercept have been published.

**Treatment**
- Prednisone 1 mg/kg PO is given for renal or severe GI disease, although benefits are not clear.
- Corticosteroids and azathioprine may be beneficial if RPGN is present. Pulse methylprednisolone Rx has also been proposed in pts w/GN, mesenteric vasculitis, or pulmonary involvement.
- NSAIDs for arthritis and arthralgias

**187 HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)**

**Definition**
Immunologic drug reaction caused by platelet-activating IgG Abs that recognize complexes of platelet factor 4 (PF4) and heparin. It is associated w/venous or arterial thrombosis.

**Diagnosis**
- HIT usually develops within 5-8 days after heparin exposure. It may develop earlier (within 2 days) in pts w/previous exposure. It may also occur up to 3 wk after exposure to heparin secondary to high titer of platelet-activating IgG induced by heparin (delayed-onset HIT).
- This dx should be differentiated from early, benign, transient thrombocytopenia that can occur w/heparin Rx. Factors favoring immune thrombocytopenia are as follows:
  - ↓ in platelet count to <100,000/mm³ or >50% of baseline value
  - The falling platelet count generally occurs after 5 days of heparin Rx or earlier if the pt had recent exposure to heparin.
• Screening can be performed w/ELISA HIT test, which detects the presence of all Ig classes (IgA, IgG, IgM) w/specificity for antigens present on a complex of PF4/heparin. The dx can be confirmed w/ELISA IgG-HIT test, which is more specific for type II HIT.

Treatment
- Discontinuation of heparin
- If warfarin had been started a few days before HIT, it should be discontinued because it has been reported to cause limb gangrene in this setting.
- Use of other anticoagulant agents. The 3 agents currently approved for HIT are
  - Danaparoid, a heparinoid compound. Approved for prophylaxis against VTE in high-risk pts w/HIT.
  - Lepirudin, a hirudin derivative. Approved for HIT w/thrombosis. Short-acting agent. Administered IV. Rx is monitored w/PTT. Excretion is renal; therefore, dose reduction is necessary in renal insufficiency.
  - Argatroban, a direct thrombin inhibitor. Approved for HIT w/thrombosis. Short-acting, administered IV. Metabolized by liver, ↓ dose in liver disease. Rx monitored w/PTT.

188 HEPATIC ENCEPHALOPATHY

Definition
Abnl mental status occurring in pts w/severe impairment of liver function and consequent accumulation of toxic products not metabolized by the liver.

Diagnosis
Classification
Hepatic encephalopathy can be classified in stages or grades 1 to 4:
- Grades 1 and 2: mild obtundation
- Grades 3 and 4: stupor to deep coma, w/ or w/o decerebrate posturing

PE
Variable w/the stage and may reveal the following abnormalities:
- Skin: jaundice, palmar erythema, spider angiomas, ecchymosis, dilated superficial periumbilical veins (caput medusae) in pts w/cirrhosis
- Eyes: scleral icterus, Kayser-Fleischer rings (Wilson’s disease)
- Breath: fetor hepaticus
- Chest: gynecomastia in men w/chronic liver disease
- Abd: ascites, small nodular liver (cirrhosis), tender hepatomegaly (congestive hepatomegaly)
- Rectal exam: hemorrhoids (portal HTN), guaiac + stool (alcoholic gastritis, bleeding esophageal varices, PUD, bleeding hemorrhoids)
- Genitalia: testicular atrophy in men w/chronic liver disease
- Extremities: pedal edema from hypoalbuminemia
- Neurologic: flapping tremor (asterixis), obtundation, coma w/ or w/o decerebrate posturing

Labs
- ALT, AST, bili, alk phos, glucose, Ca, electrolytes, BUN, Cr, alb
- CBC, platelet count, PT, PTT
- Serum and urine toxicology screen in suspected medication or illegal drug use
- Blood and urine cultures, U/A
- Venous ammonia level
- ABGs

Etiology
- Precipitating factors in pts w/underlying cirrhosis (UGI bleeding, hypokalemia, hypomagnesemia, analgesic and sedative drugs, sepsis, alkalosis, ↑ dietary protein)
- Acute fulminant viral hepatitis
- Drugs and toxins (e.g., isoniazid, acetaminophen, diclofenac, statins, methyldopa, loratadine, propylthiouracil, lisinopril, labetalol, halothane, carbon tetrachloride, erythromycin, nitrofurantoin, troglitazone)
- Reye’s syndrome
■ Shock or sepsis
■ Fatty liver of pregnancy
■ Metastatic carcinoma, HCC
■ Other: autoimmune hepatitis, ischemic veno-occlusive disease, sclerosing cholangitis, heat stroke, amebic abscesses

Treatment
■ Identification and treatment of precipitating factors
■ Restriction of protein intake (30-40 g/day) to ↓ toxic protein metabolites
■ Reduction of colonic ammonia production:
  • Lactulose 30 mL of 50% solution qid initially; dose is subsequently adjusted according to clinical response. Ornithine aspartate 9 g tid is also effective.
  • Neomycin 1 g PO q4-6h or given as a 1% retention enema solution (1 g in 100 mL of isotonic saline solution); neomycin should be used w/cautions in pts w/renal insufficiency. Metronidazole 250 mg qid may be as effective as neomycin and is not nephrotoxic; however, long-term use can be associated w/neurotoxicity. Rifamixin 1200 mg/day is a viable alternative to metronidazole.
  • A combination of lactulose and neomycin can be used when either agent is ineffective alone.
■ Treatment of cerebral edema: cerebral edema is often present in pts w/acute liver failure, and it accounts for nearly 50% of deaths. Monitoring of ICP by epidural, intraparenchymal, or subdural transducers and treatment of cerebral edema w/mannitol (100-200 mL of 20% solution [0.3-0.4 g/kg of BW]) given by rapid IV infusion is helpful in selected pts (e.g., potential transplantation pts). Dexamethasone and hyperventilation (useful in head injury) are of little value in treating cerebral edema from liver failure.

Clinical Pearls
■ The early stages of hepatic encephalopathy can be managed in the outpatient setting, whereas stages 3 and 4 require hospital admission.
■ Pts not responding to supportive Rx should be evaluated for liver transplantation.

189 HEPATITIS A

Diagnosis
H&P
■ Infection w/HAV may have acute or subacute presentation, icteric or anicteric. Severity of illness seems to ↑ w/age (90% of infection in children <5 yr may be subclinical).
■ A preicteric, prodromal phase of approximately 1-14 days; 15% no apparent prodrome. Sx are usually abrupt in onset and may include anorexia, malaise, N/V, fever, headache, abd pain.
■ Less common sx are chills, myalgias, arthralgias, upper respiratory sx, constipation, diarrhea, pruritus, urticaria.
■ Jaundice occurs in >70% of pts.
■ The icteric phase is preceded by dark urine.
■ Bilirubinuria is typically followed a few days later by clay-colored stools and icterus.

Labs (Fig. 3-23)
■ Dx confirmed by IgM anti-HAV; it is detectable in almost all infected pts at presentation and remains positive for 3-6 mo.
■ A 4× ↑ in titer of total Ab (IgM and IgG) to HAV confirms acute infection.
■ HAV detection in stool and body fluids by electron microscopy
■ HAV RNA detection in stool, body fluids, serum, and liver tissue
■ ↑ ALT and AST (usually >8× nl in acute infection)
■ ↑ Bili (usually 5-15× nl)
■ Alk phos minimally ↑ but higher level in cholestasis
■ Alb and PT are generally nl; if ↑ may herald hepatic necrosis

Imaging
■ U/S (R/O obstruction jaundice)
**Etiology**
- Caused by HAV, a 27-nm, nonenveloped, icosahedral, positive-stranded RNA virus
- Transmission is fecal-oral route, from person to person. Transmission occurs w/close contact or w/food- or water-borne outbreaks w/inadequately purified water or cooked foods.
- Parenteral transmission is considered rare.
- Vertical transmission is also reported.

**Treatment**
- Usually self-limited
- Supportive care
- Those w/fulminant hepatitis may require hospitalization and treatment of associated complications
- Activity as tolerated
- Advise to avoid alcohol and hepatotoxic drugs
- Pts w/fulminant hepatitis should be assessed for liver transplantation.

**Clinical Pearls**
- All cases of hepatitis A should be reported to the public health authorities because food-borne or water-borne outbreaks may occur, and public health efforts (mass vaccination or immunoglobulin Rx) may avert secondary cases.
- Hepatitis A is a common illness in internationally traveled and developing countries. Pretravel vaccination is strongly recommended for travelers who are HAV susceptible.
- Preexposure prophylaxis is indicated for persons traveling to endemic areas (IG 0.02-0.06 mL/kg given IM). The lower dose is effective for up to 3 mo, and the higher dose is effective for up to 5 mo.
- Postexposure prophylaxis (IG 0.02 mL/kg given IM) is indicated for persons w/recent exposure (within 2 wk) to HAV and who have not been previously vaccinated. In high-risk pts, vaccine may be administered w/immunoglobulin.
- There are several inactivated and attenuated hepatitis vaccines; only the inactivated vaccines are currently available for use, and they have been found to be safe and highly immunogenic: HAVRIX or VAQTA. These can be used in adults and children older than 12 mo. A combined hepatitis A and hepatitis B vaccine called TWINRIX is also available.
Protective Ab levels were reached in 94%-100% of adults 1 mo after the first dose. Similar results have been found for children and adolescents.

**HEPATITIS B**

**Definition**
Hepatitis B is an acute infection of the liver parenchymal cells caused by the HBV.

**Diagnosis**

**H&P**
- Often nonspecific sx
- Profound malaise
- Many asymptomatic cases
- Prodrome:
  - 15%-20% serum sickness (urticaria, rash, arthralgia) during early HBsAg
  - HBsAg-Ab complex disease (polyarteritis nodosa–arteritis, arteritis, GN)
- Hepatomegaly (87%) w/RUQ tenderness
- Hepatic punch tenderness
- Splenomegaly: rare (10%-15%)
- Jaundice, dark urine, w/occasional pruritus
- Variable fever (when present, generally precedes jaundice and rapidly declines after onset of icteric phase)
- Spider angiomas: rare; resolve during recovery
- Rare polyarteritis nodosa, cryoglobulinemia

**Labs** (Fig. 3-24)
- Acute HBV infection is best confirmed by IgM HBCab in acute or early convalescent serum or by HB DNA.
  - Generally, IgM present during onset of jaundice
  - Coexisting HBsAg
- HBsAg and IgG-HBcAb during acute jaundice are strongly suggestive of remote HBV infection and another etiology for current illness.

**Figure 3-24**. Serologic and clinical patterns observed during acute hepatitis B virus infection. Patients in whom the hepatitis B infection does not resolve (chronic carrier state) will demonstrate persistence of HBsAg and will not have an elevation of anti-HBs. ALT, alanine aminotransferase; HBeAg, hepatitis Be antigen; HBsAg, hepatitis B surface antigen; SGPT, serum glutamic pyruvic transaminase.
HBsAb alone is suggestive of immunization response.
W/recovery, HBeAg is rapidly replaced by HBeAb in 2-3 mo, and HBsAg is replaced by HBsAb in 5-6 mo.
In chronic HBV, HBsAg and HBeAg are persistent w/o corresponding Ab.
In chronic carrier state, HBsAg is persistent, but HBeAg is replaced by HBeAb.
HBCAb develops in all outcomes.
HBeAg correlation w/highest infectivity; appearance of HBeAb heralds recovery.

LFTs:
- ALT and AST: usually >8× nl at onset of jaundice (low acute ALT/AST ↑ often followed by chronic hepatitis or HCC)
- ↑ Bili: variably ↑ in icteric viral hepatitis
- Alk phos: minimally ↑ (1-3× nl) acutely

Alb and PT: Generally nl. If abnl, possible harbinger of impending hepatic necrosis (fulminant hepatitis)

WBC and ESR: generally nl or mildly increased

Imaging
U/S to R/O obstructive jaundice

Etiology
Caused by HBV (42-nm hepadnavirus w/an outer surface coat [HBsAg], inner nucleocapsid core [HbcAg; HBeAg], DNA polymerase, and partially double-stranded DNA genome)
Transmission by parenteral route (needle use, tattooing, ear piercing, acupuncture, transfusion of blood and blood products, hemodialysis, sexual contact), perinatal transmission
Infection may result from contact of infectious material w/mucous membranes and open skin breaks (e.g., HBV is stable and can be transmitted from toothbrushes, utensils, razors, baby toys, various medical equipment [respirators, endoscopes]).
Oral intake of infectious material may result in infection through breaks in the oral mucosa.
Food and water are virtually never found to be sources of HBV infection.
Infection occurs primarily in liver, where necrosis probably results from cytotoxic T-cell response, direct cytopathic effect of HbcAg (core antigen), high-level HBsAg (surface antigen) expression, or co-infection w/delta (D) hepatitis virus (RNA delta core within HBsAg envelope).
Recovery (>90%):
- Fulminant hepatitis occurs in <1% (especially if co-infected w/hepatitis D); 80% fatal.
- Unusual (5%) prolonged acute disease for 4-12 mo, w/recovery
- Overall fatality ↑ w/age and viral inoculation (e.g., transfusions)

Chronic infection (1%-2%):
- Persistent carrier state w/o hepatitis (HBsAg positive)
- Chronic persistent hepatitis (clinically well) or chronic active hepatitis (HBsAg positive and HBeAg positive)
- Cirrhosis
- HCC (especially after neonatal infection)
- Chronic infection: more common after low-dose exposure and mild acute hepatitis, w/earlier age of infection, in males, or if immunosuppressed
- 25%-33% of chronically infected will develop progressive liver disease (cirrhosis, HCC)

Treatment
**Acute Hepatitis B**
- In most cases, no treatment necessary; >90% of adults will spontaneously clear infection.
- Hospitalization is advisable for any pt in danger from dehydration caused by poor PO intake, whose PT is ↑, who has bilirubin level >15-20 µg/dL, or who has any clinical evidence of hepatic failure.
- IV Rx may be needed (rarely) for hydration during severe vomiting.
- Avoid heptatically metabolized drugs.
**Chronic Hepatitis B**

- Aim of Rx is to eradicate the virus.
- The two modalities of Rx available to achieve this goal have been immune modulators (interferon alfa) and antiviral agents in the form of nucleoside analogues (e.g., lamivudine).
- Until recently, interferon alfa given SC either qd or 3× weekly for 16-24 wk had been the mainstay of Rx. Its mechanism of action is to stimulate the immune system to attack HBV-infected hepatocytes, thus inhibiting viral protein synthesis. Currently, use of pegylated interferon alfa offers more convenient administration and more sustained viral suppression as q wk SC injection.
- A 4-mo course of treatment results in a 30%-40% response w/significant ↓ of serum HBV DNA, normalization of ALT, and loss of HBeAg. Seroconversion from HBeAg to HBeAb occurs in 15%-20%.
- Factors that ↑ the likelihood of response to interferon alfa Rx include
  - Adult onset of infection
  - ↑ Baseline ALT
  - ↓ Baseline HBV DNA
  - Absence of cirrhosis
  - Female
  - HBeAg +
- Infrequent relapse after successful completion of Rx
- 80% of pts who lose HBeAg during Rx lose HBsAg in the decade after Rx.
- >50% of pts who do not seroconvert after initial Rx develop a delayed HBeAg seroconversion months to years after Rx.
- Overall incidence of cirrhosis and HCC is ↓ in those treated w/interferon alfa.
- Interferon alfa is successful only in pts w/an active immune response; therefore, it is not effective in pts w/HIV infection and organ transplant pts.
- Asians respond poorly to interferon alfa.
- Treatment w/interferon alfa in general is also poorly tolerated. Side effects include influenza-like sx, injection-site reactions, rash, weight loss, anxiety, depression, alopecia, thrombocytopenia, granulocytopenia, thyroid dysfunction.
- Nucleoside analogues block viral replication by inhibiting HBV polymerase.
- Lamivudine was the first nucleoside analogue approved for treatment of chronic HBV infection; it has been shown to rapidly ↓ HBV replication and to suppress HBV DNA to undetectable levels after a few weeks of treatment, and treatment for 1 yr is as effective as interferon alfa w/respect to loss of HBsAg seroconversion to HBeAb and loss of HBV DNA. Emergence of resistant HBV strains while receiving Rx has limited the use of lamivudine (YMDD variants [tyrosine-methionine-aspartate-aspartate]).
- Adefovir dipivoxil is highly active against HBV and may be useful as a first-line agent or as salvage Rx for pts who are refractory or intolerant to lamivudine. (Nephrotoxicity is a potential side effect, but emergence of resistant strains is < w/lamivudine.)
- Entecavir is also approved for the treatment of hepatitis B, and it appears to be more effective and to present fewer concerns than lamivudine or adefovir regarding the emergence of resistant strains.
- Telbivudine, a thymidine nucleosidase analogue, has demonstrated greater and more consistent HBV DNA suppression than adefovir after 24 wk of treatment.
- Combination Rx w/2-3 nucleoside analogues or combination Rx w/interferon alfa is currently under investigation.
- Liver transplantation (consider for fulminant hepatitis)

**Clinical Pearls**

- Virus and HBsAg are present in high titers in blood for 1-7 wk before jaundice and for a variable time thereafter.
- Transmission is possible during entire period of HBsAg (and especially during HBeAg) in serum.
- Universal precautions should be followed for all contacts w/blood or secretions/excretions contaminated w/blood.
Diseases and Disorders

Chapter 3

H&P

Diagnosis

**Hepatitis**

**Definition**
Hepatitis is a liver disease caused by infection with hepatitis A, B, C, D, E, or non-A, non-B viruses. The term hepatitis refers to inflammation of the liver. Hepatitis can be acute or chronic.

**H&P**

- **History**
  - **Symptoms**
    - Fatigue
    - Jaundice
    - Nausea and vomiting
    - Dark urine
    - Pale stool
    - Anorexia
    - Abdominal pain
    - Fever
  - **Risk Factors**
    - Sex with an infected person
    - Injection drug use
    - Transfusion of blood or blood products
    - Sexual contact
    - Occupation
    - Household exposure
    - Travel
    - Tick bite
  - **Family History**
  - **Past History**
    - Congenital anomalies
    - Neurologic disorders
    - Blood disorders
    - Autoimmune disorders
    - Genetic disorders
    - Immune deficiencies
  - **Menstrual History**
  - **Occupational History**
  - **Educational History**
  - **Military History**
  - **Social History**
  - **Drug Use**
  - **Alcohol Use**
  - **Smoking**
  - **Exercise**
  - **Travel History**

- **Physical Exam**
  - **General**
    - General appearance
    - Body measurements
    - Skin examination
    - Head and neck examination
    - Cardiovascular examination
    - Pulmonary examination
    - Abdominal examination
    - Rectal examination
    - Genitourinary examination
    - Musculoskeletal examination
    - Neurologic examination
  - **Laboratory**
    - **LFTs**
    - **Hepatitis panel**
    - **Autoimmune serology**
    - **Immune mediated liver disease**

**Laboratory**

**Labs** (Fig. 3-25)

- **Dx** is often by exclusion because it takes 6 wk–12 mo to develop anti-HCV Ab (70% + by 6 wk, 90% + by 6 mo).
- **Diagnostic tests** include serologic assays for Abs and molecular tests for viral particles.
- **Enzyme immunoassay** is the test for anti-HCV Ab:
  - The current version can detect Ab within 4-10 wk after infection.
  - False – rate in low-risk populations is 0.5%-1%.
  - False – also in immune-compromised persons, HIV-1, renal failure, HCV-associated essential mixed cryoglobulinemia
  - False + in autoimmune hepatitis, paraproteinemia, and persons w/no risk factors
- **Recombinant immunoblot** is used to confirm + enzyme immunoassays: recommended only in low-risk settings.
- **Qualitative and quantitative HCV RNA tests using PCR**:
  - Lower limit of detection is <100 copies HCV RNA/mL.
  - Used to confirm viremia and to assess response to treatment

**Hepatitis C**

**Definition**
Hepatitis C is an acute liver parenchymal infection caused by HCV.

**Diagnosis**

- **H&P**

  - **Sx** usually develop 7-8 wk after infection (2-26 wk), but 70%-80% of cases are subclinical.
  - 10%-20% report acute illness w/jaundice and nonspecific sx (abd pain, anorexia, malaise).
  - Fulminant hepatitis may rarely occur during this period.
  - After acute infection, 15%-25% have complete resolution (absence of HCV RNA in serum, nl ALT).
  - Progression to chronic infection is common (50%-84%). 74%-86% have persistent viremia; spontaneous clearance of viremia in chronic infection is rare. 60%-70% of pts will have persistent or fluctuating ALT levels; 30%-40% w/chronic infection have nl ALT levels.
  - 15%-20% of those w/chronic HCV will develop cirrhosis during a period of 20-30 yr; in most others, chronic infection leads to hepatitis and varying degrees of fibrosis.
  - 0.4%-2.5% of pts w/chronic infection develop HCC.
  - 25% of pts w/chronic infection continue to have an asymptomatic course w/nl LFTs and benign histology.
  - In chronic HCV infection, extrahepatic sequelae include a variety of immunologic and lymphoproliferative disorders (e.g., cryoglobulinemia, membranoproliferative GN, and possibly Sjögren’s syndrome, autoimmune thyroiditis, polyarteritis nodosa, aplastic anemia, lichen planus, porphyria cutanea tarda, B-cell lymphoma, others).

- **Labs** (Fig. 3-25)

  - **Dx** is often by exclusion because it takes 6 wk–12 mo to develop anti-HCV Ab (70% + by 6 wk, 90% + by 6 mo).
  - **Diagnostic tests** include serologic assays for Abs and molecular tests for viral particles.
  - **Enzyme immunoassay** is the test for anti-HCV Ab:
    - The current version can detect Ab within 4-10 wk after infection.
    - False – rate in low-risk populations is 0.5%-1%.
    - False – also in immune-compromised persons, HIV-1, renal failure, HCV-associated essential mixed cryoglobulinemia
    - False + in autoimmune hepatitis, paraproteinemia, and persons w/no risk factors
  - **Recombinant immunoblot** is used to confirm + enzyme immunoassays: recommended only in low-risk settings.
  - **Qualitative and quantitative HCV RNA tests using PCR**:
    - Lower limit of detection is <100 copies HCV RNA/mL.
    - Used to confirm viremia and to assess response to treatment

**Prevention before exposure**:

- Lifestyle changes
- Meticulous testing of blood supply (although some chronically infected, infectious donors are HBsAg–)
- Sterilization by steam or hypochlorite
- Hepatitis B vaccine for high-risk groups given IM in deltoid to induce HBsAb (response should be confirmed) is protective (>90% effective).
- Recommendation for universal childhood immunization w/doses at birth, 1 mo, and 6 mo

**Prevention after exposure**:

- HBV hyperimmune globulin (HBIG) given immediately after needle stick, within 14 days of sexual exposure, or at birth, followed by HBV vaccination
- Standard immune globulin: nearly as effective as HBIG
- Preventive Rx w/valivudine for pts who test positive for HBsAg and are undergoing chemotherapy may ↓ the risk for HBV reactivation and HBV-associated morbidity and mortality.
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HEPATITIS C

• Qualitative PCR is useful in pts w/− enzyme immunoassay in whom infection is suspected.
• Quantitative tests use either branched-chain DNA or reverse transcription PCR; the latter is more sensitive.

Viral genotyping can distinguish among genotypes 1, 2, 3, and 4, which is helpful in choosing Rx; most of these tests use PCR. (NOTE: genotypes 1, 2, 3, and 4 predominate in the U.S. and Europe [1 is especially common in North America].)

LFTs:
• ALT and AST may be ↑ > 8× nl in acute infection; in chronic infection, ALT may be nl or fluctuate.
• Bili may be ↑ 5-10× nl.
• Alb and PT generally nl; if abnl, may be harbinger of impending hepatic necrosis.
• WBC and ESR are generally nl.

Imaging:
• U/S: useful to R/O obstructive jaundice and to evaluate rapid liver size ↓ during fulminant hepatitis or mass in HCC

Etiology
• Caused by HCV (single-stranded RNA flavivirus)
• Most HCV transmission is parenteral.
• In the U.S., advances in screening of blood and blood products have made transfusion-related HCV infection rare (the risk is estimated to be 0.001% per unit transfused).
• Injecting drug use accounts for most HCV transmission in the U.S. (60% of newly acquired cases; 20%-50% of chronically infected persons).
• Occupational needle stick exposure from an HCV-positive source has a seroconversion rate of 1.8% (range, 0%-7%).
• Nosocomial transmission rates (from surgery and procedures such as colonoscopy, hemodialysis) are extremely low.
• Sexual transmission and maternal-fetal transmission are infrequent (estimated at 5%).
• No identifiable risk in 40%-50% of community-acquired hepatitis C; but snorting of cocaine by shared use of straw or rolled-up paper has been identified as a risk factor due to microscopic bleeding of nasal mucosa.

FIGURE 3-25. Hepatitis C virus antigen and antibody. AST, aspartate aminotransferase; HCV-Ab, hepatitis C virus antibody; HCV-Ag, hepatitis C virus antigen.
HCV infection may stimulate production of cytotoxic T lymphocytes and cytokines (interferon-γ), which likely mediate hepatic necrosis.

**Treatment**

**Acute Hepatitis C**
- Supportive care
- Avoid hepatically metabolized drugs.
- Specific Rx for acute HCV infection: Studies demonstrate that *early* treatment w/interferon alfa-2b during acute HCV ↓ viral load early in infection and allows the pt’s immune system to control viral replication, thus preventing progression to chronic infection. The primary endpoint was sustained virologic response, w/absence of HCV RNA in serum 24 wk after completion of Rx.

**Chronic Hepatitis C**
- Response to Rx is influenced by HCV genotype. Pts w/genotype 1 and genotype 4 have sustained virologic response and cure rates much lower than those of pts w/genotypes 2 and 3. Cure rates for genotypes 1 and 4 are about 45%-50%, whereas cure rates for genotypes 2 and 3 are as high as 75%-80%.
- Mainstay of Rx currently is w/pegylated interferon alfa as a weekly SC injection and oral weight-based ribavirin. For genotypes 1 and 4, the Rx is for 48 wk. For genotypes 2 and 3, the length of Rx is 24 wk.
- Pegylated interferons are interferon alfa w/an attached polyethylene glycol (PEG) molecule.
- Two formulations of PEG interferon are available. Peginterferon alfa-2b (PEG INTRON) uses a weight-based dosage in a q wk SC Redipen injection. Peginterferon alfa-2a (PEGASYS) uses a fixed dosage in a q wk premixed syringe, also SC.
- Both PEG interferon alfa and ribavirin have numerous contraindications (absolute and relative) to use and may cause a variety of side effects. Interferon alfa can cause influenza-like sx, thrombocytopenia, granulocytopenia, rash, alopecia, anorexia, psychiatric disturbances, others. Ribavirin can cause hemolysis, nausea, anemia, nasal congestion, pruritus. Ribavirin is contraindicated in pregnancy, and pts should not get pregnant while receiving Rx and for 6 mo after Rx.
- In pts who fail to respond to interferon alfa and ribavirin, <10% will respond to re-treatment.
- Liver transplantation:
  - Hepatitis C is the main indication for liver transplantation in the U.S.
  - It is the only option for pts w/deteriorating HCV-related cirrhosis and for some pts w/HCC.
  - Recurrent infection occurs in almost all pts w/progressive fibrosis and cirrhosis; up to 20% progress to cirrhosis within 5 yr after transplantation.
- Co-infection w/HIV: these pts have a poor response to pegylated interferon alfa and ribavirin if the immune system is depleted, w/low CD4 count as seen in the AIDS category. It is, however, important to treat pts co-infected w/HIV and hepatitis C w/HAART. Many co-infected pts are stable from their HIV disease but have significant morbidity and mortality from their hepatitis C.

**Clinical Pearls**
- Progression of disease is more rapid in pts who drink alcohol regularly, pts of advanced age at time of infection, and those co-infected w/other viruses (HIV, HBV).
- No preventive vaccine available; postexposure immune globulin provides min. protection.
- Preventive measures include use of universal precautions, careful screening of blood and blood products, lifestyle changes.
- Eltrombopag is an orally active thrombopoietin-receptor agonist that stimulates thrombopoiesis. It has been reported effective in increasing platelet counts in pts w/thrombocytopenia due to HCV-related cirrhosis.
Regression of cirrhosis has been demonstrated after antiviral Rx in some pts w/chronic hepatitis C. Regression is associated w/↓ disease-related morbidity and improved survival.

**Hepatitis, Autoimmune**

**Definition**

Chronic inflammatory condition of the liver, characterized by the presence of circulating auto-Abs. Three types have been described:

- Type I or “classic” autoimmune hepatitis is the most predominant form in the U.S. and is positive for either ANA or ASMA. There is a bimodal age distribution: teenagers and adults between 50-70 yr are most commonly affected.
- Type II is rare in the U.S. and primarily affects young children. Type II is characterized by the presence of Abs to liver-kidney microsomes (anti-LKM).
- Type III is characterized by Abs to soluble liver antigen or liver-pancreas antigen (anti-SLA/LP). There is also a bimodal age distribution associated w/type III.

**Diagnosis**

**H&P**

- Sx may include fatigue, anorexia, nausea, abd pain, pruritus, and arthralgia.
- Jaundice
- Hepatomegaly/splenomegaly
- Autoimmune findings may include arthritis, xerostomia, keratoconjunctivitis, cutaneous vasculitis, and erythema nodosum
- For pts presenting w/advanced disease: ascites, edema, abnl bleeding, jaundice

**Labs**

- ↑ ALT, AST
- Bili and alk phos moderately ↑/nl
- Hypergammaglobulinemia usually present
- Circulating auto-Abs often present:
  - RF
  - ANA: present in 2/3 of pts. Typical pattern is homogeneous or speckled. Titer does not correlate w/the stage, activity, or prognosis
  - ASMA: present in 87% of pts. Titer does not correlate w/course or prognosis
  - Anti-LKM: typically found in pts who are ANA− and ASMA−. Found in <1/25 pts in U.S. Present in pediatric population and up to 20% of adults in Europe; also present in pts w/drug-induced hepatitis.
  - Anti-SLA/LP: present in 10%-30% of pts. Associated w/higher rate of relapse after corticosteroid Rx. Several studies suggest that pts w/anti-SLA/LP have a more severe course.
- Hypoalbuminemia and ↑ PT w/advanced disease
- Liver bx reveals interface hepatitis, which consists of a lymphoplasmacytic inflammatory infiltrate that extends from the portal tract into the lobule.

**Imaging**

- U/S of liver and biliary tree: r/o obstruction or hepatic mass

**Etiology**

- Exact etiology unknown; liver histology demonstrates cell-mediated immune attack against hepatocytes.
- Presence of a variety of auto-Abs suggests an autoimmune mechanism.
- Strong genetic predisposition

**Treatment**

**Initial Treatment**

- Prednisone 60 mg PO/day or combination treatment w/prednisone 30 mg PO/day + azathioprine 50 mg PO/day
- Combination Rx allows lower prednisone doses and less steroid side effects.
- Goal of Rx is remission (normalization of gamma globulin and bili, ↓ of aminotransferases to <2× upper limit of nl).
Indications for Treatment

- AST >10× upper limit of nl
- AST >5× upper limit of nl, w/serum gamma globulin level 2× upper limit of nl
- Young age
- Histologic features of bridging necrosis or multiacinar necrosis

Evaluation of Treatment Response

- Goal is normalization of AST.
- Pts who normalize their AST may continue to have ongoing active hepatitis involving inflammation and fibrosis. 5%-10% of pts w/nl transaminase levels progress to cirrhosis.
- Histologic improvement may lag behind clinical and laboratory improvement by as much as 6 mo.
- Repeated liver bx should be considered after normalization of transaminase levels.

Clinical Pearls

- 65% of pts achieve remission by 18 mo; 80% achieve remission by 3 yr.
- Approximately 10% of pts fail to improve w/Rx.
- Complete normalization on bx is associated w/15%-20% risk of relapse.
- Persistent interface hepatitis is associated w/90% risk of relapse.
- Pts w/decompensated cirrhosis usually do not benefit from corticosteroid Rx and should be considered for liver transplantation.

**HEPATOCELLULAR CARCINOMA (HCC)**

Definition

Malignant tumor of the hepatocytes.

Diagnosis

H&P

- ½ of pts are asymptomatic at diagnosis. Abd pain may be initial presentation.
- Signs of underlying cirrhosis are often present.
- Previously compensated cirrhosis w/new ascites, encephalopathy, jaundice, or bleeding
- Paraneoplastic syndromes (hypoglycemia, erythrocytosis, hypercalcemia, severe diarrhea) may be present.

Labs

- ↑ LFTs
- ↑ AFP in 70% of pts (sensitivity 40%-65%; specificity 80%-94%)
- Paraneoplastic syndromes associated w/HCC may cause hypercalcemia, hypoglycemia, and polycythemia.
- ↑ HBV DNA level (≥10,000 copies/mL) is a strong risk predictor of HCC independent of HBeAg, serum aminotransferase level, and liver cirrhosis.

Imaging

- U/S, CT scan, or MRI
- Multiphasic CT and MR scans are usually performed when there is a focal lesion on U/S or strong clinical suspicion of HCC.
- Percutaneous bx under U/S or CT scan usually is diagnostic. Tissue dx is the gold standard. However, HCC can be reliably diagnosed when
  - Mass >2 cm that shows characteristic arterial vascularization is seen on 2 imaging modalities or
  - Single positive imaging method w/AFP >200 µg/mL

Staging

According to the Barcelona Clinic Liver Cancer staging classification, treatment is determined according to stage:

- Early stage: asymptomatic single tumor ≤5 cm or 3 nodules, each ≤3 cm (known as Milan criteria)
- Intermediate stage: pts w/tumors that exceed early criteria but do not yet show cancer-related sx, vascular invasion, or mets
- Advanced stage: pts w/cancer-related sx
- End stage: pts w/advanced, symptomatic disease
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**Treatment**
- Early stage: curative treatment (surgical resection or liver transplantation). Pts who have a single lesion can be offered surgical resection if they are noncirrhotic or have cirrhosis but still have well-preserved liver function. Liver transplantation is an effective option for pts w/HCC corresponding to the Milan criteria. Local ablation is safe and effective Rx for pts who cannot undergo resection or as a bridge to transplantation.
- Intermediate stage: optimal therapeutic approach is controversial. Outcome may be improved w/chemoembolization.
- Advanced stage: no curative treatment. In the absence of metastatic disease or portal invasion, chemoembolization is reasonable. Entry into clinical trials should be considered.
- End stage: palliative care.
- For pts w/unresectable HCC, chemoembolization with cisplatin or doxorubicin has been shown to improve 2-yr survival rates. Trials reveal that in pts w/advanced HCC, median survival and the time to radiologic progression was ↑ by nearly 3 mo w/treatment w/sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor and platelet-derived growth factor receptor.

**HEPATORENAL SYNDROME (HRS)**

**Definition**
Syndrome of intense renal vasoconstriction resulting from loss of renal auto-regulation occurring as a complication of severe liver disease. There are 2 types of HRS:
- Type 1: progressive impairment in renal function as defined by a doubling of initial serum Cr concentration above 2.5 mg/dL in <2 wk
- Type 2: stable or slowly progressive impairment of renal function not meeting the criteria for type 1

**Diagnosis**
Criteria for HRS are
- Serum Cr >1.5 mg/dL or 24-hr CrCl <40 mL/min
- Absence of shock, ongoing infection, and fluid loss, and no current treatment w/nephrotoxic drugs
- Absence of sustained improvement in renal function (↓ in serum Cr to ≤1.5 mg/dL after discontinuation of diuretics and a trial of plasma expansion)
- Absence of proteinuria (<500 mg/day) or hematuria (<50 RBC/high-power field)
- Absence of U/S evidence of obstructive uropathy or parenchymal renal disease
- Urinary Na <10 mmol/L

**Etiology**
- HRS may occur after significant ↓ of effective blood volume (e.g., paracentesis, GI bleeding, diuretics) or in the absence of any precipitating factors.

**Treatment**
- Volume challenge (to ↑ MAP) followed by large-volume paracentesis (to ↑ CO and ↓ renal venous pressure) is recommended to distinguish HRS from prerenal azotemia in pts w/Fena <1%. In pts w/prerenal azotemia, the ↑ in renal perfusion pressure and renal blood flow will result in prompt diuresis; the volume challenge can be accomplished by giving a solution of 100 g of alb in 500 mL of isotonic saline.
- Vasopressin analogues may improve renal perfusion by reversing splanchnic vasodilation, which is the hallmark of HRS. IV norepinephrine in combination w/alb and furosemide may also be effective.
- Rx w/vasoconstrictors for 5-15 days in attempt to ↓ serum Cr to <1.5 mg/dL w/one of the following drugs or drug combinations:
  - Norepinephrine (0.5-3.0 mg/hr IV)
  - Midodrine (7.5 mg PO tid, ↑ to 12.5 mg tid if needed) in combination w/octreotide (100 µg SC tid, ↑ to tid PRN)
Herpes Zoster

Definition
Herpes zoster is a disease caused by reactivation of the varicella-zoster virus. After the primary infection (chickenpox), the virus becomes latent in the dorsal root ganglia and re-emerges when there is a weakening of the immune system (secondary to disease or advanced age).

Diagnosis
- Pain generally precedes skin manifestation by 3-5 days and is generally localized to the dermatome that will be affected by the skin lesions.
- Constitutional sx are often present (malaise, fever, headache).
- The initial rash consists of erythematos maculopapules generally affecting one dermatome (thoracic region in majority of cases); some pts (<50%) may have scattered vesicles outside of the affected dermatome.
- The initial maculopapules evolve into vesicles and pustules by the third or fourth day.
- The vesicles have an erythematous base, are cloudy, and have various sizes (a distinguishing characteristic from herpes simplex, in which the vesicles are of uniform size).
- The vesicles subsequently become umbilicated and then form crusts that generally fall off within 3 wk; scarring may occur.
- Pain before, during, and after the rash is generally significant.
- Secondary bacterial infection w/S. aureus or Streptococcus pyogenes may occur.
- Regional lymphadenopathy may occur.
- Herpes zoster may involve the trigeminal nerve (most frequent cranial nerve involved); involvement of the geniculate ganglion can cause facial palsy and a painful ear, w/vesicles on the pinna and external auditory canal (Ramsay Hunt syndrome).

Treatment
- PO antivirals can ↓ acute pain, inflammation, and vesicle formation when treatment is begun within 48 hr of onset of rash. Treatment options are:
  - Acyclovir 800 mg 5× qd for 7-10 days
  - Valacyclovir 1000 mg tid for 7 days
  - Famciclovir 500 mg tid for 7 days
- Immunocompromised pts should be treated w/IV acyclovir 500 mg/m² or 10 mg/kg q8h in 1-hr infusions for 7 days, w/close monitoring of renal function and adequate hydration; vidarabine (continuous 12-hr infusion of 10 mg/kg/day for 7 days) is also effective for treatment of disseminated herpes zoster in immunocompromised hosts.
- Pts w/AIDS and transplant pts may develop acyclovir-resistant varicella-zoster; these pts can be treated w/foscarnet (40 mg/kg IV q8h) continued for ≥10 days or until lesions are completely healed.
- Wet compresses (using Burow’s solution or cool tap water) applied for 15-30 min, 5-10×/day, are useful to break vesicles and to remove serum and crust.
- Corticosteroids should be considered in older pts within 72 hr of clinical presentation or if new lesions are still appearing (if there are no contraindications). Initial dose is prednisone 40 mg/day ↓ by 5 mg/day until finished. When used, there is a ↓ in the use of analgesics and time to resumption of usual activities, but there is no effect on the incidence and duration of postherpetic neuralgia.
Hospitalization and IV acyclovir in pts w/disseminated herpes zoster
Pts w/herpes zoster ophthalmicus should be evaluated by an ophthalmologist.
Postherpetic neuralgia Rx:
  • Gabapentin 100-600 mg tid
  • Lidocaine patch 5% applied to intact skin to cover the most painful area for up to 12 hr within a 24-hr period
  • Capsaicin cream 3-5x qd for several weeks after the crusts have fallen off
  • Sympathetic blocks (stellate ganglion or epidural) w/0.25% bupivacaine and rhizotomy: reserved for severe cases unreasonable to conservative treatment

**Vaccination**
Immunocompetent adults ≥60 years of age are appropriate candidates for a single dose of varicella-zoster vaccine (VZV) whether or not they have had a previous episode of herpes zoster. Immunization w/VZV (Zostavax) boosts waning immunity in older adults and ↓ the severity and duration of pain caused by herpes zoster by 61%. Adults who are VZV seronegative (never had varicella) should be immunized against varicella w/2 doses of varicella vaccine (Varivax).

**196 HISTOPLASMOSIS**

**Definition**
Infection caused by the fungus *Histoplasma capsulatum*. It is characterized by a primary pulmonary focus w/occasional progression to chronic pulmonary histoplasmosis (CPH) or various forms of dissemination. Progressive disseminated histoplasmosis (PDH) may present w/a diverse clinical spectrum, including adrenal necrosis, pulmonary and mediastinal fibrosis, and ulcerations of the oropharynx and GI tract. In those pts co-infected w/HIV, it is a defining disease for AIDS.

**Diagnosis**
Conidia are deposited in alveoli, then converted to yeast forms that spread to regional lymph nodes and other organs, especially liver and spleen.
1-2 wk later, a granulomatous inflammatory response begins to contain the yeast in the form of discrete granulomas.
Delayed-type hypersensitivity to *Histoplasma* antigens occurs 3-6 wk after exposure.

**H&P**
Clinical disease is manifested in various forms, depending on host cellular immunity and inoculum size:
Acute primary pulmonary histoplasmosis
  • Overwhelming number of pts are asymptomatic.
  • Most clinically apparent infections are manifested by complaints of fever, headache, malaise, pleuritic chest pain, nonproductive cough, and weight loss.
  • <10%, mainly women, complain of arthralgias, myalgias, and skin manifestations such as erythema multiforme or erythema nodosum.
  • Acute pericarditis presents in smaller percentage of pts.
  • Hepatosplenomegaly is most commonly observed in children.
  • W/particularly heavy exposure, there is severe dyspnea, marked hypoxemia, impending respiratory failure.
  • Most pts are asymptomatic within 6 wk.
CPH
  • Presents insidiously w/low-grade fever, malaise, weight loss, cough, sometimes w/blood-streaked sputum or frank hemoptysis
  • Most pts w/cavitary lesions present w/associated COPD or chronic bronchitis, masking underlying fungal disease.
  • Tends to worsen preexisting pulmonary disease and further contribute to eventual respiratory insufficiency
PDH
  • In both acute and subacute forms, constitutional sx of fever, fatigue, malaise, and weight loss are common.
• Acute form (seen in infants and children) presents with respiratory sx, fever ≥101°F (38.3°C), generalized lymphadenopathy, marked hepatosplenomegaly, and fulminant course resembling septic shock associated with a high fatality rate.
• Subacute form is more common in adults and associated with lower temperatures, hepatosplenomegaly, oropharyngeal ulceration, focal organ involvement (including adrenal destruction, endocarditis, chronic meningitis, and intracerebral mass lesions).
• Course of subacute form is relentless; untreated pts die within 2 yr.
• Chronic PDH is found in adults and marked by gradual sx of weight loss, weakness, easy fatigability; low-grade fever when present; oropharyngeal ulcerations and hepatomegaly and/or splenomegaly in ≥2/3 of pts.
• Less clinical evidence of focal organ involvement in chronic form than in subacute form.
• Natural h/o chronic form protracted and intermittent, spanning months to years.

■ Histoplasmosa
  • A healed area of caseation necrosis surrounded by a fibrous capsule
  • Usually asymptomatic

■ Mediastinal fibrosis
  • A rare consequence of a fibroblastic process that encases caseating mediastinal lymph nodes, producing severe retraction, compression, and distortion of mediastinal structures
  • Constriction of the bronchi resulting in bronchiectasis, also esophageal stenosis associated with dysphagia and SVC syndrome

■ Presumed ocular histoplasmosis syndrome (POHS)
  • Dx characterized by distinct clinical features, including atrophic choroidal scars and maculopathy in pt w/hx suggestive of exposure to the fungus (e.g., residence in an endemic area)
  • Pt complains of distortion or loss of central vision w/o pain, redness, or photophobia.
  • Usually no evidence of infection except for a positive skin reaction to histoplasmin

■ In pts w/AIDS
  • Possible presentation as overwhelming infection similar to acute PDH seen in children
  • Constitutional sx: fever, weight loss, malaise, cough, dyspnea
  • About 10% w/cutaneous maculopapular, erythematous eruptions, or purpuric lesions on face, trunk, and extremities
  • Up to 20% w/CNS involvement, manifested as intracerebral mass lesions, chronic meningitis, or encephalopathy

Labs
■ Demonstration of organism on culture from body fluid or tissues to make definitive dx
  • Especially high yield in pts w/AIDS
  • Characteristic oval yeast cells in neutrophils w/Giemsa stain from peripheral smear
  • Preparations of infected tissue w/Gomori’s silver methenamine for revealing yeast forms, especially in areas of caseation necrosis

■ Serologic tests, including complement-fixing (CF) Abs and immunodiffusion assays

■ Detection of Histoplasma antigen in urine: may be influenced by infections w/Blastomyces and Coccidioides

■ In PDH
  • Pancytopenia
  • ↑↑ in alk phos, ALT common

■ In chronic meningitis (majority of cases)
  • CSF pleocytosis w/either lymphocytes or neutrophils predominating
  • ↑ CSF protein levels
  • Hypoglycorrachia
**Imaging**

- CXR in acute pulmonary histoplasmosis
  - Single or multiple patchy infiltrates, especially in the lower lung fields
  - Hilar or mediastinal lymphadenopathy w/ or w/o pneumonitis
  - Diffuse nodular or confluent bilateral miliary infiltrates characteristic of heavier exposure
  - Infrequent pleural effusions, except when associated w/pericarditis
- CXR in histoplasmosa: coin lesion displaying central calcification, ranging from 1-4 cm in diameter, predominantly located in the subpleural regions
- CXR in CPH:
  - Upper lobe disease frequently associated w/cavities
  - Preexisting calcifications in the hilum associated w/peribronchial streaking extending to the parenchyma
- CXR in acute PDH: hilar adenopathy or diffuse nodular infiltrates
- CT scan of adrenals to reveal bilateral enlargement and low-attenuation centers

**Etiology**

- *H. capsulatum* is a dimorphic fungus present in temperate zones and river valleys worldwide.
- In the U.S., it is highly endemic in southeastern, mid-Atlantic, and central states.
- It exists as mold at ambient temperature and favors soils enriched w/bird or bat droppings.

**Treatment**

- No drug Rx is required for asymptomatic pulmonary disease.
- A course of Rx w/ketoconazole 400 mg/day or itraconazole 200 mg/day PO for 3-6 wk may be beneficial in some pts w/acute pulmonary distress. Avoid fluconazole because it is not as active.
- Same Rx appropriate for immunocompetent, mild to moderately symptomatic pts w/CPH and subacute and chronic forms of PDH, but duration for 6-12 mo
- Amphotericin B 0.7-1 mg/kg IV for 6-12 mo in pts hypersensitive to or intolerant of azole Rx
- Amphotericin B for life-threatening disease or continued illness as a result of primary failure or relapse of adequate azole Rx. A lipid formulation of amphotericin B can be used to avoid nephrotoxicity.
  - For acute pulmonary histoplasmosis associated w/ARDS, acute PDH, and *Histoplasma* meningitis: dose of 0.7-1 mg/kg IV >4 hr
  - Endpoint of Rx for pt w/complicated acute pulmonary disease: total dose of 500 mg
  - Endpoint for pt w/acute PDH: total dose 35 mg/kg or 2.5 g total
  - Prednisone 60-80 mg/day beneficial for severe fungal hypersensitivity complicating acute pulmonary disease
- Endocarditis: surgical treatment w/excision of infected valve or graft combined w/amphotericin for a total dose of 35 mg/kg or 2.5 g
- For pericardial disease:
  - Antifungal Rx: no apparent benefit
  - Best managed w/NSAIDs
- For POHS:
  - Antifungal Rx: no apparent benefit
  - May respond to laser Rx
- In pts w/AIDS: lifelong suppressive Rx w/either itraconazole, given 200 mg PO qd, or IV amphotericin B at a dose of 50 mg once weekly. A triazole compound, posaconazole (400 mg PO bid), may be useful in refractory cases, but clinical experience is limited at this point.

**Clinical Pearls**

- *H. capsulatum*, variety *duboisii*, also known as African histoplasmosis, is restricted to Senegal, Nigeria, Zaire, and Uganda.
- Unlike with *H. capsulatum*, pulmonary forms of *duboisii* are not seen, and the disease is limited to the skin, soft tissues, and bone.
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197 HIV/AIDS
Powel H. Kazanjian

The Asymptomatic HIV-Infected Patient
Natural Hx, Testing, and Case Definition

- Acute infection occurs 2-6 wk from the time of viral transmission.
  - It most often is a self-limited mononucleosis-like illness: pharyngitis, rash, splenomegaly, and lymphadenopathy, occasionally w/hepatitis and aseptic meningitis.
  - The p24 antigen and the HIV PCR are detected; HIV serology first becomes + 1 mo later.
- 3 HIV viral Ab screening tests currently are in use:
  - ELISA: 99.9% sensitive. False – may result when measured in the acute infection period (sensitivity, 99.9%).
  - Rapid serologic screening HIV antigen–coated gelatin or latex particle agglutination assays: less sensitive and specific than standard ELISA tests.
  - Western blot confirmatory test: performed when ELISA is +. Identifies specific viral antigens.
    - + when both core and envelope antigens are present.
    - Indeterminate when either antigen is present—a false + result if unchanged during 6 mo.
- Early stage (CD4 cells >400/mm³): diffuse lymphadenopathy may be present. ↑ Levels of viral replication, 10⁹ copies/day, occur at this stage even though the pt remains asymptomatic.
- Middle stage (CD4 cells, 200–400/mm³)
  - M. tuberculosis infections, recurrent herpes zoster, persistent mucocutaneous herpes simplex infections, and recurrent bacteremias caused by S. pneumoniae and Salmonella sp occur.
  - Kaposi’s sarcoma and the oral candidiasis and hairy leukoplakia appear.
- AIDS: advanced HIV infection (CD4 cell count <200/mm³). The classic opportunistic infections PCP, cerebral toxoplasmosis, cryptococcosis occur when CD4 cell count <200/mm³; infections due to CMV and MAC occur when CD4 cell count <500/mm³.

Management Strategies

- Initial testing: CD4 cell count and HIV viral load measured q3-6 mo to guide decisions about antiretroviral use and prophylaxis against PCP and MAC infection.

- Other testing: identifies latent infections that may become reactivated because of loss of T-cell function but can be prevented by the use of specific agents.
  - Serology to Toxoplasma gondii (IgG): clinical infection may be prevented by TMP-SMZ used as prophylaxis for PCP.
  - VDRL test. LP should be performed in pts w/a confirmatory specific test (FTA). Rx w/IM benzathine PCN if the CSF formula is nl, and IV PCN × 10 days if the CSF VDRL test is reactive or CSF pleocytosis, protein ↑, or hypoglycorrachia is present.
  - PPD skin test showing induration of ≥5 mm, or pts w/exposure to someone w/active TB. Treat w/INH 300 mg/day for 9 mo or, in case of INH-induced hepatitis, rifampin 600 mg PO qd (only for those not receiving PIs or NRTIs) × 4 mo.
  - Immunizations: pts should receive the annual influenza vaccine each fall. Pneumococcal polysaccharide vaccine is recommended for all pts w/HIV infection and is most effective in those w/CD4 counts >200. Invasive pneumococcal infections occur w/↑ frequency in HIV-infected pts; these pts should be revaccinated every 5 yr. Hepatitis B vaccination is recommended for pts who have no evidence of prior infection. They should also receive hepatitis A vaccine.

Prophylactic Agents

Prophylaxis for several opportunistic infections can be discontinued if there has been a sustained CD4 cell count ↑ >200 associated w/HAART (PCP, toxoplasmosis, cryptococcosis) and 100 for MAC for more than 3-6 mo.
Diseases

**HIV/AIDS**

Chapter

Infections due to *T. gondii, Nocardia* spp, and enteric pathogens:

- Adverse reactions to TMP-SMZ (GI distress, fever, rash, and leukopenia): occur in 40%-60%; discontinuation of drug may be necessary.
- Dapsone indicated w/TMP-SMZ rash; 30% w/TMP-SMZ toxicity develop reaction to dapsone.
- Aerosolized pentamidine, 300 mg/mo, and atovaquone, 750 mg bid, are third-line agents.

Prophylaxis against MAC in pts w/CD4 cell counts >75: azithromycin 1200 mg weekly is the most effective agent.

**Highly Active Antiretroviral Therapy (HAART)**

- Treatment goals are maximal and durable suppression of viral loads (<50 copies/mL), restoration of immunologic function (CD4 cell count), and prevention of HIV disease progression.
- Agents in 6 separate drug classes are now available—NRTIs, NNRTIs, PIs, fusion inhibitors, co-receptor inhibitors, and integrase inhibitors.
- The standard regimen is 2 NRTI (TNF/3TC) plus an NNRTI (efavirenz [Sustiva]) or a ritonavir-boosted PI agent (lopinavir, atazanavir, fosamprenavir).
- Treatment should be offered to pts w/acute infection and chronic HIV infection after the CD4 cell count declines <350 but before it reaches 200. Before treatment is initiated or changed, pts should be educated about expected side effects and a closely scheduled follow-up visit ↑ adherence.
- After initiation of HAART, measure CD4 counts and viral loads at 1 and 4 mo. The criteria used to assess initial HAART efficacy are as follows:
  - >1.0 log ↓ in HIV viral load within 4 wk and undetectable viral load (HIV RNA <50 copies/mL) within 4 mo
  - CD4 boost >25 cells ↑ above pretreatment value or >200 absolute value within 6 mo after initiation of Rx
- Pts should be evaluated roughly q3mo and more often when indicated to assess CD4 and VL responses. A new regimen should be initiated in pts whose initial regimen has failed (rebound viremia).
- Drug resistance testing should be performed when there is HAART failure; a new regimen should be selected on the basis of antiviral hx and absence of mutations to HAART-included agents on resistance testing. Once resistance develops to an agent in one class, cross-resistance to other drugs in the same class frequently occurs.
- An ideal regimen should include preferably 3 agents from 2 separate drug classes to which the virus retains susceptibility. Agents frequently included in a new regimen include the following:
  - Enfuviride (90 mg SC bid), an HIV entry fusion inhibitor now infrequently used because of inconvenience and reactions (injection site reactions)
  - Raltegravir (400 mg bid): an integrase inhibitor
  - Maraviroc inhibits viral binding to co-receptor CCR5. A viral tropism assay must be first measured before initiation to ensure that the virus is an R5 strain.
  - Etravirine (200 bid): an NNRTI to which certain NNRTI-resistant strains (K103N mutants) remain susceptible
  - Darunavir/ritonavir (600/100 bid): a PI to which certain PI-resistant strains remain susceptible
- NRTI agents and their toxicities:
  - NRTIs other than 3TC, TNF, and ABAC may cause lactic acidosis, a complication that can range in severity from asymptomatic elevations to a fatal condition.
  - Zidovudine (Retrovir, AZT) 300 mg bid [often used in a combination tablet w/3TC (Combivir)]. Transient myalgias, headache, and fatigue (common). Macrocystosis occurs commonly but does not interfere w/Rx. Myopathy is rare. Hematologic toxicity (leukopenia and anemia): related to HIV disease status.
  - Tenofovir (TNF, Viread) 300 mg/day: may be combined w/3TC or FTC. Nephrotoxicity is the major adverse reaction, w/declines in GFR of 8% during a 12- to 18-mo period.
- Lamivudine (Epivir, 3TC) 150 mg bid: adverse reactions occur no more frequently than when AZT or D4T is used as monotherapy.
- Emtricitabine (FTC) 200 mg qd has adverse reactions similar to those with 3TC.
- Didanosine (Videx, ddI) 200 mg bid, or 400 mg enteric-coated tablet once qd. Pancreatitis (10%); ddI should be stopped if clinical or chemical pancreatitis occurs (amylase elevation >2.5× the baseline value). Peripheral neuropathy (15%): characterized first by dysesthesias, numbness, and hyporeflexia, is reversible w/prompt discontinuation of ddI.
- Abacavir (Ziagen) 300 mg bid; combined w/3TC (Epzicom, 1 tablet qd). The risk of abacavir hypersensitivity ↑ to 8% in pts w/HLA-B5701 genotype. Testing for the haplotype would ↓ the incidence of the adverse reaction from 9% to 2%.
- Zalcitabine (Hivid, ddC) 0.75 mg tid. Rarely used because of relative lack of potency and tid schedule.

### NNRTI agents and their toxicities:
- Nevirapine (Viramune) 200 mg bid: begin w/200 mg qd × 2 wk before beginning bid dose. Rash, which is usually transient and resolves w/o discontinuation of the agent, occurs in 10% of pts. Hepatic transaminase elevations occur most commonly during the first 18 wk of Rx. Nevirapine should not be used in women w/CD4 cell counts >250 and men w/CD4 cell counts >400 because of risks of severe hepatotoxicity in this setting.
- Efavirenz (Sustiva) 600 mg every night: transient neurologic or psychiatric sx—insomnia, dizziness, or impaired concentration—occur in 50% of pts. The sx may progress and require discontinuation of the drug. Delusions and acute depression may also occur. Transient rash may also occur but rarely requires discontinuation of the drug. This agent should not be used in pregnancy because malformations in developing animal (monkey) fetuses have been described.
- Delavirdine (Rescriptor) 400 mg tid is not frequently used as it has antiviral activity that is not as potent as that of the other NNRTI agents. Transient rash develops in 30% of pts.

### PIs (in combination w/low-dose ritonavir) and their toxicities:
- The PIs have multiple drug interactions that result from their elimination by P-450 CYP3A.
- Metabolic complications associated w/all PI agents:
  - All agents in this class may lead to insulin resistance, fat accumulation, lipoatrophy, and lipid disturbances. Fat atrophy of the extremities and face and accumulation in the abd or posterior neck may occur 1-2 yr after the start of Rx.
  - Serum cholesterol and lipid abnormalities may occur. In addition to dietary changes (↑ fiber content of the diet along w/↓ the amount of saturated and hydrogenated fat), Rx w/statins may be necessary.
  - Changes in glucose metabolism, leading to DM, and exacerbation of preexisting DM
  - The incidence of CAD is ↑ in pts experiencing hyperlipidemia and hyperglycemia because these are risk factors for heart disease.
  - Osteonecrosis and osteoporosis: routine measurements of bone density among asymptomatic pts are not recommended, but pts should be advised to have an adequate intake of Ca and vitamin D.
- Ritonavir (Norvir): most PI-containing regimens are combined w/ritonavir (100 mg bid), a potent inhibitor of CYP3A4, to boost the concentration of that particular PI.
- Lopinavir/ritonavir (Kaletra) 400 mg bid/100 mg bid or 800/200 mg qd. Because of its low-toxicity profile relative to older PI agents and its potency, lopinavir/ritonavir is a first-choice PI agent.
- Atazanavir (Reyataz)/ritonavir 300 mg PO qd/100 mg qd: GI side effects rare. Because it does not lead to significant changes in cholesterol or TGs, it offers the potential advantage of engendering less hyperlipidemia than other ritonavir-boosted PIs.
• Tipranavir (TPR)/ritonavir 500/200 bid. This nonpeptidic PI has activity against isolates that are resistant to other PIs. Its toxicity profile is similar to that of lopinavir/ritonavir.
• Fosamprenavir/ritonavir 1400/200 qd. It has efficacy comparable to that of other PIs.
• Saquinavir/ritonavir (1000 mg bid/100 mg bid) and indinavir/ritonavir 800 mg bid/100 mg bid and nelfinavir (Viracept) 1250 mg bid are now rarely used PI agents; they are not as potent as the preceding agents.

Occupational exposure to HIV. The transmission rate of HIV after an exposure w/o antiviral use is low—0.3%. AZT/3TC/PI is indicated for pts w/high-risk exposures (visible blood on device causing injury from a known HIV-infected person w/high viral load), preferably within 24 hr of exposure.

• HIV in pregnancy
  • The goals of HAART in pregnant women are to provide Rx for the mother and to ↓ vertical transmission (in utero or perinatally). Rx should be initiated during the second trimester.
  • Efavirenz is not recommended for women in their first trimester of pregnancy.
  • Similarly, nevirapine is not recommended as the NNRTI component for pregnant women who have <250 CD4 cells.

Possible strategies to improve adherence
• Several strategies can be used to improve adherence, which is critical to maintain >95% to prevent resistance and to maintain durability of the regimen.
• Depression or substance abuse should be treated before Rx is initiated (except when antiretroviral treatment is urgently needed), and tools such as pill boxes, alarms, and charts should be provided.

Treatment of Symptomatic Patient with AIDS-Defining Illness
The use of HAART in pts w/active opportunistic infections may be complicated by the immune reconstitution inflammatory syndrome (IRIS). IRIS usually involves constitutional sx along w/local reactions 1-2 mo after HAART. Nonetheless, when both infections are diagnosed simultaneously, particular antimicrobial treatment for the opportunistic infection diagnosed should be started immediately and HAART should not be delayed, especially in those w/low CD4 cell counts. IRIS may be managed w/anti-inflammatory agents while maintaining both the particular antimicrobial agent and HAART Rx.

Fungal Disorders
• Candida infection (thrush) may involve mucous membranes of the mouth.
  • Dx: by clinical appearance—whitish patches w/erythematous base; potassium hydroxide preparation may demonstrate budding yeast and pseudohyphae.
  • Diff dx: herpes simplex and aphthous ulcers (painful), oral hairy leukoplakia (as a result of EBV)
  • Rx: clotrimazole troches 5x/day × 10 days: refractory cases may require 10 days of oral fluconazole (100 mg/day).
• Esophagitis/oropharyngeal candidiasis is usually present when there is odynophagia or dysphagia.
• DDx: EBV, CMV, giant esophageal ulcers, and cancer, which should be considered in those pts not responding to antifungal Rx.
• Rx: fluconazole 100 mg PO bid × 3 wk
• Cryptococcus (neoformans) infection
• Pts may have headache, fever, AMS, meningismus (only 30%) w/cranial nerve palsies; Cryptococcus may disseminate to lungs, skin, blood, liver, and prostate. Nuchal rigidity may be absent. Dx is made by spinal fluid analysis; head CT scan should be performed first. Spinal WBC, glucose, and protein levels may all be nl. Cryptococcal antigen is the most sensitive (>1:16 in 95% cases). Serum cryptococcal antigen is reactive in more than 90% of pts w/CNS involvement.
• Initial Rx is w/amphotericin B (0.7 mg/kg/day) for 2 wk w/adjunctive flucytosine (100 mg/kg/day), unless preexisting cytopenias prohibit its use. Serum flucytosine levels must be monitored. Maintenance oral fluconazole Rx (200-400 mg/day) prevents relapse and may be withdrawn when HAART-restored CD4 is >200.
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**Mycobacterial Infections**

- **Mycobacterium avium**
- **Mycobacterium tuberculosis**
- **Pneumocystis**
- **Histoplasmosis**
- **Coccidioidomycosis**

- Pts extrapulmonary
- Initial Rx
- After discontinuation
- Discontinuation
- Caution

**Recommendations**

- Itraconazole
- Fluconazole
- PO
- TMP-SMZ
- Atovaquone
- Primaquine
- TMP-SMZ
- Pentamidine
- Trimetrexate
- Methenamine
- 3-wk course.
- Once daily.
- 35 mm Hg
- 200 mg PO bid.
- 200 mg PO bid.
- 200 mg PO bid.
- 15-30 mm Hg.
- 15-30 mm Hg.
- PO regimen:
- PO regimen:

**PO regimens:**

- Rx in mild cases (PO <70 mm Hg)
- A gradient, <35 mm Hg)
- a 3-wk course.
- 15 mg/kg/day in 3 divided doses
- 150 mg/kg/day and dapsone 100 mg/day
- glucose-6-phosphate dehydrogenase deficiency w/dapsone
- glucose-6-phosphate dehydrogenase deficiency
- 30 mg/day and dapsone
- 450 mg PO qid

**Atovaquone** (may be less effective than TMP-SMZ 750 mg PO tid

**IV regimens if moderate-to-severe (PO <70 mm Hg or A-a gradient >35 mm Hg)***

- TMP-SMZ 15 mg/kg/day in 3 individual doses
- 3 mg/kg/day; may need to observe for hypotension, pancreatitis, hypoglycemia, and azotemia
- 45 mg/m² once qd for pts intolerant of or refractory to TMP-SMZ or pentamidine; must be given w/leucovorin

**Adjunctive corticosteroid Rx** indicated when PO is <70 mm Hg or A-a gradient is >35 mm Hg to prevent early deterioration of oxygenation by inflammation. There is a risk of reactivation of latent infection (CMV, histoplasmosis, tuberculosis) w/steroid use.

**Mycobacterial Infections**

- **Mycobacterium tuberculosis** may cause pulmonary involvement, extrapulmonary involvement, or both. Extrapulmonary tuberculosis may involve meningitis, lymphadenitis, or peritonitis. W/more advanced disease (CD4 <200), there may be atypical CXR findings (e.g., nonapical involvement).

- Caution is required for the use of TB meds and HAART. Rifampin should be substituted w/rifabutin w/the use of PIs and NNRTIs. Saquinavir hardgel should not be given w/rifabutin; PIs (indinavir, nelfinavir, amnpeanavir) require dosage modifications.

- HIV-infected pregnant women w/+ PPD test reaction or exposure to active TB should be considered for chemoprophylaxis. Isoniazid w/pyridoxine is the recommended Rx.

- **Mycobacterium avium** complex (MAC)

- Sx are fever, night sweats, and wasting. Dissemination may involve lymph nodes, liver, and bone marrow, causing marrow suppression, diarrhea w/abd pain, gastroenteritis, and, rarely, pulmonary involvement.
Dx is made by blood culture (special lysis-centrifugation technique), which takes an average of 3 wk; cultures of tissue or bone marrow are rarely necessary to make the dx.

- Combination Rx w/at least 2 agents:
  - Clarithromycin 500 mg PO bid (azithromycin, 500 mg/day PO, is alternative)
  - Ethambutol 15 mg/kg/day PO. Addition of a third agent (rifabutin) may be considered.
- Medications to be considered in pts who have had relapsing disease are rifabutin, ciprofloxacin, and amikacin. Rifabutin 300 mg/day or ciprofloxacin 500-750 mg bid can be used as third agents.

**Bacterial Infections**

Pts w/HIV may develop infections from *S. pneumoniae, H. influenzae,* or *P. aeruginosa.* Fever w/productive cough and lobar infiltrates may occur. Functional humoral response to *S. pneumoniae* may be impaired, leading to recurrent infections caused by these pathogens. Other pathogens include the following:

- *Salmonella spp:* recurrent bacteremia; treat w/ampicillin, TMP-SMZ, ciprofloxacin, or third-generation ceph, based on sensitivities and clinical presentation; GI sx may not be present. Avoid raw or undercooked eggs, poultry, meat, and seafood.
- *Listeriosis:* in HIV-infected individuals who are severely immunosuppressed. Soft cheeses and ready-to-eat foods (hot dogs, cold cuts) should be avoided or heated until steaming hot.
- *Sinusitis:* may be routine bacterial infection or involve *P. aeruginosa* or fungi.
- *Bacillary angiomatosis:* an infection involving skin, w/red lesions that can be mistaken for Kaposi’s sarcoma; can involve viscera (liver, spleen, bone); caused by *Rochalimaea henselae* or *R. quintana*; treat w/erythromycin or doxycycline; other potential bacterial pathogens in HIV are *Rhodococcus equi,* which may cause cavitating pneumonia, and *Nocardia.*

**Viral Infections**

- Herpes simplex
  - May involve mucous membranes, cause genital herpes, or cause rectal or perirectal infection, resulting in proctitis
  - Initial Rx: acyclovir 200 mg PO 5×/day × 10 days; recurrent episodes may need treatment w/400 mg PO 3-5×/day × 7 days or until clinically resolved. IV foscarnet or cidofovir can be used for acyclovir-resistant isolates of HSV.
- HCV
  - Pts w/HIV infection should be tested for HCV by enzyme immunoassay. If test result +, confirm w/RIBA or PCR for HCV RNA.
  - Pts w/HCV and HIV should receive vaccination for hepatitis A if they are negative for hepatitis A Abs.
  - Pts w/HIV-HCV co-infection are at ↑ risk for chronic liver disease and should be evaluated for treatment by providers w/experience in treating both HIV and HCV.
- CMV: infection from this virus may cause illness involving the retina, GI tract (including esophagus, colon), and CNS.
  - Chorioretinitis may develop in 25% of AIDS pts and also may be unilateral, w/viremia involving other organs; the pt usually reports ↓ vision or “floaters”; ophthalmologic evaluation may be necessary to confirm dx.
  - Esophagitis: deep ulcerations are seen, confirmed by the presence of inclusion bodies by bx.
  - Colitis: usually associated w/diarrhea, weight loss, and fever; occurs in approximately 10% of AIDS pts.
  - CNS encephalitis or polyradiculopathy (areflexic paraplegia)
  - Rx: 3 agents are available. Rx may be discontinued if HAART-restored CD4 cell counts are >200.
  - Retinitis: ganciclovir implant is effective in delaying progression of disease; oral valganciclovir is used to prevent systemic manifestations of disease.
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- Ganciclovir: induction dose, 5 mg/kg bid × 14 days, followed by 5 mg/kg/day indefinitely for retinitis; may cause granulocytopenia or neutropenia related to dose, which is compounded by the use of AZT and possibly by other antiretroviral medications.
- Foscarnet: induction dose, 60 mg/kg q8h IV for 2-3 wk; dosing depends on CrCl and requires adjustment; maintenance Rx is 90-120 mg/kg q24h.
- Cidofovir: 5 mg/kg weekly for 2 wk, then every other week as maintenance.

- Progressive multifocal leukoencephalopathy: demyelinating disease most often involving posterior cortex of brain, resulting in slowly progressive cognitive impairments. Clinical and radiologic improvement or, in some cases, complete resolution may occur w/HAART-associated restoration of CD4 cell counts.

Parasitic Infections

- Toxoplasmosis
  - Sx of Toxoplasma encephalitis: headache, fever, encephalopathy, focal neurologic deficits. Pneumonia, myocarditis, and retinal involvement occur less often.
  - Dx is usually presumptive, based on multifocal ring-enhancing and hypodense mass lesions on CT, + toxoplasmic IgG serology, and a clinical and radiologic response to antitoxoplastic Rx. Other causes of CNS mass lesions in AIDS pts include CNS lymphoma, fungal infection (Aspergillus, Cryptococcus), tuberculoma, bacterial abscess.
  - Treatment
    - Pyrimethamine + sulfadiazine: pyrimethamine 100-200 mg loading dose, followed by 50 mg/day PO; sulfadiazine 1-1.5 g PO q6h as initial treatment, followed by a maintenance dose of pyrimethamine 25 mg/day, sulfadiazine 500 mg q6h
    - Clindamycin: 600-1200 mg IV or 600 mg PO q6h (2.4g/day) and pyrimethamine 50 mg/day PO
    - Atovaquone, TMP-SMZ, and macrolides may have anti-Toxoplasma properties and can be considered alternative treatments.

- Cryptosporidiosis: protozoal infection causing watery diarrhea, abd pain, and dehydration, particularly worse in pts w/CD4 counts <50. Dx is made by a modified AFB stain of stool. There is no effective Rx for HIV-infected pts, although nitazoxanide has been used in immunocompetent pts. Azithromycin, when taken for MAC prophylaxis, may ↓ the risk for cryptosporidiosis.

- Isosporiasis: another protozoal infection w/a presentation similar to that of Cryptosporidium infection, w/oocysts found in routine stool stain; Rx w/Bactrim 1 DS tablet qid × 10 days is followed by maintenance.

- Microsporidiosis: also similar to Cryptosporidium infection, w/oocysts found in special modified trichrome stain of stool; treatment w/albendazole (400 mg bid) is effective only against certain species; atovaquone is effective against others.

Malignant Neoplasms

Malignant neoplasms may be occurring more frequently, as prognosis has been improved w/HAART and prevention of opportunistic infections w/prophylactic Rx. The following have been listed as AIDS-defining malignant neoplasms:

- Kaposi’s sarcoma: found most often in HIV-infected homosexual men and less frequently (<5%) in pts in other HIV risk groups. The lesions from Kaposi’s sarcoma may be multifocal, involving skin (79%), lymph nodes (70%), GI tract (45%), and lungs (10%). Treatment is based on extent of involvement; Rx w/intralesional vinblastine and w/radiation Rx is recommended for localized or small numbers of lesions, and chemotherapy w/vincristine and vinblastine, etoposide, or bleomycin for aggressive and disseminated disease. Use of many interleukins (e.g., interleukin-4), tumor necrosis factor, and pentoxifylline is investigational.

- Non-Hodgkin’s lymphoma: a B-cell tumor associated w/EBV; most often extranodal; 30% may occur in pts w/CD4 cell counts >200; GI tract, CNS, bone marrow, or liver (or other viscera in smaller percentages) are also
affected. Regimens of M-BACOD have approximately 50% response. Dose-limiting multiagent Rx is myelosuppression.

- Primary CNS lymphoma: most occur in pts w/CD4 counts <200, but \( \frac{1}{2} \) occur w/CD4 counts >200. Most are unifocal ring-enhancing mass lesions that cause focal neurologic deficits or seizures. Brain bx establishes dx.
- AIDS-related cervical cancer: associated w/HPV; often in pts w/multiple sexual partners and possibly related to primary association of HIV to cancer development.
- Other cancers associated w/HIV infection:
  - Hodgkin’s lymphoma: may occur in a pt who is an IV drug user or who has STD. EBV may be linked to both Hodgkin’s disease and NHL; pts usually present w/disseminated stage III or stage IV disease involving bone marrow (50%) or liver and lungs.
  - Anal carcinoma: associated w/HPV and impaired immunity; ↑ risk in homosexual men.

**AIDS-Related Cachexia**

- Megestrol acetate can ↑ appetite and food intake in pts w/AIDS-related weight loss. It can result in a statistically significant weight gain and in pt-reported improvement in overall sense of well-being.

### 198 HODGKIN’S LYMPHOMA

**Definition**

Malignant disorder of lymphoreticular origin, characterized histologically by the presence of multinucleated giant cells (Reed-Sternberg cells) usually originating from B lymphocytes in germinal centers of lymphoid tissue.

**Diagnosis**

**H&P**

- Palpable lymphadenopathy, generally painless, is the most common presenting sx.
- Most common site of involvement: neck region
- Fever and night sweats: fever in a cyclical pattern (days or weeks of fever alternating w/febrile periods) is known as Pel-Epstein fever.
- Weight loss, generalized malaise
- Persistent, nonproductive cough
- Pain associated w/alcohol ingestion, often secondary to heavy eosinophil infiltration of the tumor sites, is relatively uncommon.
- Pruritus
- Others: SVC syndrome, spinal cord compression (rare), erythema nodosum, ichthyosis

**Labs**

- Dx is confirmed w/lymph node bx. The WHO classifies Hodgkin’s lymphoma into 2 groups: classic Hodgkin’s lymphoma (92%-97%) and nodular lymphocyte-predominant Hodgkin’s lymphoma (3%-8%). In classic Hodgkin’s lymphoma, there are four main histologic subtypes, based on the number of lymphocytes, Reed-Sternberg cells, and the presence of fibrous tissue:
  - Nodular sclerosis (60%-80%)
  - Mixed cellularity (15%-30%)
  - Lymphocyte predominance (2%-7%)
  - Lymphocyte depletion (1%-6%)
- Nodular sclerosis occurs mainly in young adulthood, whereas the mixed cellularity type is more prevalent after age 50 yr.

**Staging**

- Detailed H&P (w/documentation of “B sx”)
- Surgical bx
- Labs (CBC, ESR, BUN, Cr, alk phos, LFTs, alb, LDH, uric acid)
- CT scan of chest, abd, pelvis, neck
- PET scan
- Staging for Hodgkin’s disease follows the Ann Arbor staging classification.
  - Stage I: Involvement of a single lymph node region
  - Stage II: 2 or more lymph node regions on the same side of the diaphragm
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- Stage III: Lymph node involvement on both sides of diaphragm, including spleen
- Stage IV: Diffuse involvement of external sites
- Suffix A: No systemic sx
- Suffix B: Presence of fever, night sweats, or unexplained weight loss of 10% or more BW during 6 mo
- Suffix X: indicates bulky disease \( \geq \frac{1}{2} \) widening of mediastinum or >10 cm max dimension of nodal mass on CXR

**Treatment**
- Stage I and II: radiation Rx alone (involved-field radiotherapy [35 Gy]) unless a large mediastinal mass is present (mediastinal to thoracic ratio \( \geq 1.3 \)); in the latter case, a combination of chemotherapy and radiation Rx may be used.
- Stage IB or IIB: total nodal irradiation is often used, although chemotherapy is performed in many centers.
- Stage IIIA: treatment is controversial. It varies w/the anatomic substage after splenectomy.
- IIIA and minimum splenic involvement: radiation Rx alone may be adequate.
- IIIA or IIIA w/extensive splenic involvement: there is disagreement whether chemotherapy alone or a combination of chemotherapy and radiation Rx is the preferred treatment modality.
- IIIB and IVB: the treatment of choice is chemotherapy w/ or w/o adjuvant radiotherapy.
- Various regimens can be used for combination of chemotherapy. Many oncologists prefer the combination of doxorubicin + bleomycin + vincristine + dacarbazine (ABVD).
- Advanced Hodgkin’s disease: ↑dose bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP).
- Monoclonal Ab Rx: SGN-30 and MDX-060 and rituximab have shown promising results.

**HORNER’S SYNDROME**

**Definition**
Clinical triad of ipsilateral ptosis, miosis, and sometimes anhidrosis of the face. These physical findings are the result of disruption of the cervical sympathetic pathway along its course from the hypothalamus to the eye. Disruption of any of the 3 neurons involved in the pathway (central, preganglionic, or postganglionic) can cause Horner’s syndrome.

**Diagnosis**

**H&P**
- Ptosis results from loss of sympathetic tone to eyelid muscles.
- Miosis results from loss of sympathetic pupillodilator activity. The affected pupil reacts normally to light and accommodation. Anisocoria is greater in darkness.
- The presence of anhidrosis is variable and depends on the site of injury in the sympathetic pathway. Anhidrosis may occur w/lesions affecting the central or preganglionic neurons.
- Conjunctival or facial hyperemia may occur on the affected side because of loss of sympathetic vasoconstrictor activity.
- In congenital Horner’s syndrome, the iris on the affected side may fail to become pigmented, resulting in heterochromia of the iris, w/the affected iris remaining blue-gray.

**Imaging**
- Chest CT scan: r/o lung tumors
- MRI of the head and neck: r/o lesions affecting the central and cervical sympathetic pathway
- U/S, CTA, or MRA: assess the vessels in the head and neck

**Etiology**
Lesions affecting any of the neurons involved in the sympathetic pathway can cause Horner’s syndrome.
Mechanical:
- Syringomyelia
- Trauma
- Benign tumors
- Malignant tumors (thyroid, Pancoast tumor)
- Metastatic tumor
- Lymphadenopathy
- Neurofibromatosis
- Cervical rib
- Cervical spondylosis

Vascular (ischemia, hemorrhage, or AVM):
- Brainstem lesion: commonly occlusion of the posterior inferior cerebellar artery but almost any of the vessels may be responsible (vertebral; superior, middle, or inferior lateral medullary arteries; superior or anterior inferior cerebellar arteries).
- Internal carotid artery aneurysm or dissection. Injury of other major vessels (carotid artery, subclavian artery, ascending aorta) can also cause Horner’s syndrome.
- Cluster headache, migraine

Miscellaneous:
- Congenital
- Demyelination (MS)
- Infection (apical TB, herpes zoster)
- Pneumothorax
- Iatrogenic (angiography, internal jugular/subclavian catheter, chest tube, surgery, epidural spinal anesthesia)
- Radiation

Treatment
- Treatment depends on underlying cause.

Clinical Pearl
- Prognosis depends on underlying cause. Horner’s syndrome is an uncommon presentation for malignant disease. In one study, 60% of cases were idiopathic.

200 HYDROCEPHALUS, NORMAL PRESSURE (NPH)

Definition
Syndrome of symptomatic hydrocephalus in the setting of nl CSF pressure. The classic clinical triad of NPH includes gait disturbance, cognitive decline, and incontinence.

Diagnosis
H&P
- Gait difficulty: pts often have difficulty initiating ambulation, and the gait may be broad-based and shuffling, w/the appearance that the feet are stuck to the floor (i.e., “magnetic gait” or “frontal gait disorder”).
- Cognitive decline: mental slowing, forgetfulness and inattention w/oagnosia, aphasia, or other “cortical” disturbances
- Incontinence: initially may have urinary urgency; later incontinence develops. On occasion, fecal incontinence also occurs.

Labs
- LP

Imaging
- CT scan or MRI: to document ventriculomegaly. The distinguishing feature of NPH is ventricular enlargement out of proportion to sulcal atrophy.
- MRI has advantages over CT, including better ability to visualize structures in the posterior fossa, to visualize transependymal CSF flow, and to document extent of white matter lesions.

Etiology
- Approximately 50% of cases are idiopathic; remaining cases are from secondary causes, including prior subarachnoid hemorrhage, meningitis, trauma, and intracranial surgery.
- Sx are presumed to result from stretching of sacral motor and limbic fibers that lie near the ventricles, as dilation occurs.
Treatment
Neurosurgical referral for shunting in appropriate pts. Factors that may predict positive outcome w/surgery are:
- NPH secondary to prior trauma, subarachnoid hemorrhage, or meningitis
- H/o mild impairment in cognition <2 yr
- Onset of gait abnormality before cognitive decline
- Imaging demonstrates hydrocephalus w/o sulcal enlargement
- Transependymal CSF flow visualized on MRI

HYDRONEPHROSIS

Definition
Dilation of the renal pyelocalyceal system, most often as a result of impairment of urinary flow.

Diagnosis
H&P
- Pain caused by distention of collecting system or renal capsule. It can vary in location from flank to lower abd to testes/labia.

Imaging
- U/S (90% sensitive and specific)
- Abd CT scan w/o IV contrast: provides excellent localization of the site of obstruction

Etiology
Mechanical Impairments:
- Congenital: ureteropelvic junction narrowing, ureterovesical junction narrowing, ureterocele, retrocaival ureter, bladder neck obstruction, urethral valves, urethral stricture, meatal stenosis
- Acquired:
  - Intrinsic to urinary tract: calculi, inflammation, trauma, sloughed papillae, ureteral tumor, blood clots, prostatic hypertrophy or cancer, bladder cancer, urethral stricture, phimosis
  - Extrinsic to urinary tract: gravid uterus, retroperitoneal fibrosis or tumor (e.g., lymphoma), aortic aneurysm, uterine fibroids, trauma (surgical or nonsurgical), PID, pelvic malignant neoplasms (e.g., prostate, colorectal, cervical, uterine, bladder)

Functional Impairments
- Neurogenic bladder (often w/autonomic ureter) can occur w/spinal cord disease or diabetic neuropathy.
- Pharmacologic agents such as α-adrenergic antagonists and anticholinergic drugs can inhibit bladder emptying.
- Vesicoureteral reflux may occur.
- Pregnancy can cause hydrourter and hydronephrosis (right more often than left) as early as the second month. Hormonal effects on ureteral tone combine w/mechanical factors.

Treatment
- Urgent treatment is required if urinary tract obstruction is associated w/UTI, ARF, or uncontrollable pain.
- Conservative management of calculi w/IV fluid, IV abx (if evidence of infection), and aggressive analgesia may be enough to treat acute unilateral urinary tract obstruction, depending on the size (90% of stones <5 mm will pass spontaneously).
- Urethral catheter is adequate to relieve most obstructions at or distal to the bladder, but a suprapubic catheter will occasionally be required (e.g., impassable urethral stricture or urethral injury). Neurogenic bladder may require intermittent clean catheterization if frequent voiding and pharmacologic treatments are ineffective.
- Nephrostomy tube can be placed percutaneously to facilitate urinary drainage.
- ESWL is used to fragment large stones to facilitate spontaneous passage or subsequent extraction (note: ESWL is contraindicated in pregnancy).
- Nephroscopy is performed for extraction of proximal stones under direct vision.
Cystoscopy w/ureteroscopy is used for removal of distal ureteral stones with use of a loop or basket w/ or w/o fragmentation by ultrasonic or laser lithotripsy.

Ureteral stents can be used for extrinsic and some intrinsic ureteral obstructions.

Urethral dilation or internal urethrotomy can be used for urethral strictures.

Nephrectomy or ureteral diversion may be required in severe cases (e.g., malignant neoplasm).

Ureterovesical reimplantation can be used for reflux disease.

TURP is used for severe obstruction from BPH.

**IV fluid and electrolyte replacement**

### 202 HYPERALDOSTERONISM (ALDOSTERONISM)

#### Definition

Primary aldosteronism is a clinical syndrome characterized by hypokalemia, HTN, ↓ PRA, and ↑ aldosterone secretion.

#### Diagnosis

In pts w/hypokalemia and ↓ PRA, confirming tests for primary hyperaldosteronism include the following:

- 24-hr urine test for aldosterone and potassium levels (potassium >40 mEq and aldosterone >15 µg).
- Captopril test: administration of 25-50 mg of captopril and measurement of plasma renin and aldosterone levels 1-2 hr later. A plasma aldosterone level >15 ng/dL confirms the dx of primary aldosteronism. This test is more expensive and is best reserved for situations in which the 24-hr urine for aldosterone is ambiguous.
- 24-hr urinary tetrahydroaldosterone (<65 µg/24 hr) and saline infusion test (plasma aldosterone >10 ng/dL) can also be used in ambiguous cases.
- The renin-aldosterone stimulation test (posture test) is helpful in differentiating idiopathic hyperaldosteronism (IHA) from aldosterone-producing adenoma (APA). Pts w/APA have a ↓ in aldosterone levels at 4 hr, whereas pts w/IHA have an ↑ in their aldosterone levels.
- As a screening test for primary aldosteronism, an ↑ plasma aldosterone-renin ratio (ARR), drawn randomly from pts taking HTN drugs, is predictive of primary aldosteronism (positive predictive value 100%). ARR is calculated by dividing plasma aldosterone (mg/dL) by PRA (mg/mL/hr). ARR >100 is considered elevated.
- Bilateral adrenal venous sampling may be done to localize APA when adrenal CT scan is equivocal. In APA, ipsilateral/contralateral aldosterone level is >10:1, and ipsilateral venous aldosterone concentration is very high (>1000 ng/dL).
- MRI or adrenal CT (w/3-mm cuts) may be used to localize neoplasm.
- Adrenal scanning w/iodocholesterol (NP-59) or 6-β-iodomethyl-19-norcholesterol after dexamethasone suppression. The uptake of tracer is ↑ in those w/aldosteronoma and absent in those w/idiopathic aldosteronism and adrenal carcinoma.

#### Etiology

- Aldosterone-producing adenoma (>60%)
- Idiopathic hyperaldosteronism (>30%)
- Glucocorticoid-suppressible hyperaldosteronism (<1%)
- Aldosterone-producing carcinoma (<1%)

#### Treatment

- Control of BP and hypokalemia w/spironolactone, amiloride, or ACEIs
- Surgery (unilateral adrenalectomy) for APA

### 203 HYPERCALCEMIA

#### Definition

Serum Ca level >10.3 mg/dL.
### Diagnosis

**H&P**
- GI: constipation, anorexia, N/V, pancreatitis, ulcers
- CNS: confusion, obtundation, psychosis, lassitude, depression, coma
- GU: nephrolithiasis, renal insufficiency, polyuria, ↓ urine-concentrating ability (nephrogenic DI), nocturia, nephrocalcinosis
- Musculoskeletal: myopathy, weakness, osteoporosis, pseudogout, bone pain
- Other: HTN, metastatic calcifications, band keratopathy, pruritus
- Most pts are asymptomatic at the time of dx.

**Hx:**
- FHx of hypercalcemia such as MEN syndromes or familial hypocalciuric hypercalcemia (the latter is a benign autosomal dominant condition of ↑ serum Ca\(^{2+}\), ↓ urinary Ca, ↓ fractional excretion of Ca\(^{2+}\) [generally <1%], and a nl PTH; parathyroidectomy is not indicated).
- Inquire about intake of milk and antacids (milk-alkali syndrome), intake of thiazides, lithium, large doses of vitamins A or D.
- Inquire whether pt has any bone pain (MM, metastatic disease) or abd pain (pancreatitis, PUD).

**PE:**
- Look for evidence of primary neoplasm (e.g., breast, lung).
- Check eyes for evidence of band keratopathy (found in medial and lateral margin of the cornea).

### Labs (Fig. 3-26)
- Initial labs: serum Ca, alb, PO\(_4\)\(^{3-}\), Mg, alk phos, electrolytes, BUN, Cr, PTH, and 24-hr urine Ca collection. In pts w/abnl alb levels, it is important to

![Flowchart](image-url)

**FIGURE 3-26.** Diagnostic algorithm for hypercalcemia.
measure the serum level of ionized Ca to correct for the abnl alb. If the ionized Ca is not available, the total Ca can be corrected for a low alb level by adding 0.8 mg/dL to the total Ca level for every 1.0 g/dL of serum alb below the level of 3.5 g/dL.
- If the hx is suggestive of ↑ intake of vitamin D (e.g., in food faddists w/intake of megadoses of fat-soluble vitamins), a serum vitamin D level (1,25-dihydroxyvitamin D) is indicated.
- The iPTH distinguishes primary hyperparathyroidism from hypercalcemia caused by malignant disease when the serum Ca level is >12 mg/dL; below this value, there is considerable overlap, and the differentiation between these two major causes of hypercalcemia is extremely difficult.
- Urinary cyclic adenosine monophosphate is strongly suggestive of primary hyperparathyroidism, although certain nonparathyroid malignant neoplasms also produce ↑ levels of urinary cyclic adenosine monophosphate. PTH-like protein (PTHrP) is ↑ in most pts w/ hypercalcemia-associated malignant neoplasms. It can be measured when the dx of humoral hypercalcemia of malignancy is uncertain on clinical grounds.

Imaging
- Bone survey may show evidence of subperiosteal bone resorption (suggesting PTH excess).
- Parathyroid localization w/technetium Tc 99 sestamibi has a high sensitivity and specificity for single adenomas.
- ECG: shortening of the QT interval

Etiology
- Malignant disease: hypercalcemia has been reported to occur in up to 20%-30% of pts w/cancer at some time during the course of their disease. It can be classified into 4 types:
  - Humoral hypercalcemia of malignancy (80%). Commonly seen w/breast cancer, MM, and lymphoma. It is due to the secretion of PTH-related protein (PTHrP) by the tumors. It causes ↑ bone resorption and renal retention of Ca.
  - Local osteolytic hypercalcemia (<20%). Most often seen w/squamous cell cancer (e.g., lung, head and neck, esophagus), renal or ovarian cancer, breast cancer, some lymphomas, and endometrial cancer. The hypercalcemia is due to ↑ osteoclastic bone resorption in areas surrounding the malignant cells within the marrow space.
  - Secretion of 1,25(OH)2D by lymphomas (<1%) resulting in ↑ osteoclastic bone resorption and ↑ intestinal absorption of Ca
  - Ectopic hyperparathyroidism (<0.01%): due to ectopic secretion of PTH
- Hyperparathyroidism: ↑ bone resorption, GI absorption, and renal absorption because of
  - Parathyroid hyperplasia, adenoma
  - Hyperparathyroidism or renal failure w/secondary hyperparathyroidism
  - Granulomatous disorders: ↑ GI absorption (e.g., sarcoidosis)
  - Paget’s disease: ↑ bone resorption, seen only during periods of immobilization
  - Vitamin D intoxication, milk-alkali syndrome: ↑ GI absorption
  - Thiazides: ↑ renal absorption
  - Other causes: familial hypocalciuric hypercalcemia, thyrotoxicosis, adrenal insufficiency, prolonged immobilization, vitamin A intoxication, recovery from ARF, lithium administration, pheochromocytoma, SLE

Treatment
Acute Severe Hypercalcemia (serum Ca >13 mg/dL or symptomatic pt)
- Vigorous IV hydration w/NS. Usual administration rate is 200-500 mL/hr, depending on the baseline level of dehydration, renal function, and the CV and mental status of the pt.
- NS infusion will ↑ urinary Ca excretion by inhibiting proximal tubular sodium and Ca reabsorption.
- Use NS solution w/caution in pts w/cardiac or renal insufficiency to avoid fluid overload.
Diseases

Chronic Hypercalcemia

**Medications:**

- **Unless**:
  - Glucocorticoids: hydrocortisone, 3–5 mg/kg/day IV initially, then prednisone, 30 mg PO bid.
  - The Ca-lowering action of corticosteroids occurs through ↓ intestinal Ca absorption; they are effective in treating hypercalcemia secondary to breast carcinoma, myeloma, sarcoidosis, and vitamin D intoxication.
  - Their use in pts w/acute hypercalcemia is limited because it takes 48–72 hr before the serum Ca level shows a significant ↓.

- **If**:
  - Discontinue:
  - Identify:
  - Second-line agents:
    - Calcitonin: 4 U/kg q12h: used only as a second-line agent because its reductions are small and transient.
      - The initial dose is given IV after initial skin testing for allergy; subsequent doses may be given SC.
      - It may be useful in cases of hypercalcemia associated w/ hyperphosphatemia because it also ↑ urinary phosphate excretion.
    - Mithramycin: 25 μg/kg in 500 mL of D₅W infused during 6 hr; this is the most potent of all antihypercalcemic agents. It is generally used as a second-line agent because its use is limited by potential side effects.
      - It ↓ serum Ca within 12–24 hr by inhibiting bone resorption.
      - Its use should be restricted to emergency treatment of severe hypercalcemia.
      - May cause hepatotoxicity, nephrotoxicity, and thrombocytopenia (usually seen after repeated IV doses) and should not be used in cases of renal failure or hepatic dysfunction and in pts w/bleeding diathesis.
    - Loop diuretics (e.g., furosemide 20–40 mg IV) can worsen dehydration and should not be administered until full hydration has been achieved. Thiazide diuretics are contraindicated because they will stimulate rather than inhibit renal Ca reabsorption.

**Chronic Hypercalcemia**

- Identify and treat underlying disease (e.g., vitamin D intoxication, sarcoidosis).
- Discontinue potential hypercalcemic agents (e.g., thiazide diuretics).
- If the hypercalcemia is caused by a parathyroid adenoma, parathyroidectomy is the treatment of choice if the following pertains:
  - Serum Ca level >1 mg/dL above reference range
  - Presence of complications from primary hyperparathyroidism (e.g., nephrolithiasis, bone disease)
  - Episode of life-threatening hypercalcemia
  - Severe hypercalciuria (>400 mg/24 hr)
  - ↓ Bone mass (T score <2)
  - Age >50 yr
  - If surgery is not performed, pts should be observed for development of complications and indications for surgery.
- Unless contraindicated, pts w/chronic hypercalcemia should maintain ↑ daily intake of fluids (3–5 L/day) and of sodium chloride (>400 mEq/day) to ↑ renal Ca excretion.
- Medications:
  - Glucocorticoids: hydrocortisone, 3–5 mg/kg/day IV initially, then prednisone, 30 mg PO bid.
  - The Ca-lowering action of corticosteroids occurs through ↓ intestinal Ca absorption; they are effective in treating hypercalcemia secondary to breast carcinoma, myeloma, sarcoidosis, and vitamin D intoxication.
  - Their use in pts w/acute hypercalcemia is limited because it takes 48–72 hr before the serum Ca level shows a significant ↓.
• Oral phosphates: 1-3 g/day in divided doses (e.g., Neutra-Phos, 250-500 mg PO q6h)
  • Phosphates ↓ serum Ca by ↓ GI Ca absorption and bone resorption.
  • Oral phosphates are not useful in pts w/acute hypercalcemia because their Ca-lowering effect will not be apparent for 2-3 days.
  • Oral phosphates are contraindicated in pts w/renal insufficiency or any other medical conditions w/elevated serum phosphate levels.
  • Indomethacin (prostaglandin synthetase inhibitor) 75-150 mg/day is useful in pts w/prostaglandin-mediated hypercalcemia.

204 HYPERCOAGULABLE STATE

Definition
Inherited or acquired condition associated w/↑ risk of thrombosis.

Diagnosis
Hx
A hypercoagulable state is strongly suggested by
■ Spontaneous thrombosis: absence of other medical conditions associated w/↑ risk of thrombosis
■ <50 yr of age at first episode of thrombosis
■ FHx of thrombosis: first-degree relative w/thrombosis at <50 yr
■ Recurrent thrombotic events
■ Thrombosis in unusual anatomic location (i.e., portal, hepatic, mesenteric, or cerebral vein)
■ Thrombosis in pregnancy, post partum, or associated w/OCP use
■ Warfarin-induced skin necrosis
■ Adverse pregnancy outcomes may also be associated w/thrombophilia: recurrent pregnancy loss, preeclampsia, placental abruption, intrauterine growth restriction

PE
■ Inherited thrombophilia is usually associated w/VTE, most commonly DVT
■ Some acquired thrombophilies are associated w/arterial thrombosis.
■ Pregnancy complications
■ Medical conditions associated w/↑ risk of thrombosis

Tests
■ CBC w/peripheral smear, electrolytes, renal and LFTs, PT/PTT, PSA (in men >50 yr), U/A
■ Activated protein C resistance (APCR) assay (using factor V–deficient plasma); if +, confirm w/genetic test for FVL mutation; use genetic test in pregnancy and if lupus anticoagulant is present.
■ Prothrombin G20210A mutation: genetic test
■ Antithrombin deficiency: functional assay (antithrombin-heparin cofactor assay)
■ Protein C deficiency: functional assay (activity): may be falsely low in the presence of APCR, ↑ factor VIII level, or lupus anticoagulant
■ Protein S deficiency: functional assay (activity) and immunoologic assay (free and total level). Functional assay may be falsely ↓ in the presence of APCR, ↑ factor VIII level, or lupus anticoagulant.
■ APS: any of the following found on 2 occasions at least 12 wk apart: lupus anticoagulant or ACL (IgG and IgM) or anti–β2-glycoprotein 1 Ab (IgG and IgM)
■ Hyperhomocysteinemia: fasting plasma homocysteine level (if nl but suspicion is ↑, can proceed w/methionine loading test and genotyping for methylene tetrahydrofolate reductase)
■ Factor VIII level: functional assay

Imaging
■ As appropriate to diagnose thrombosis and to r/o medical conditions associated w/↑ thrombotic risk

Etiology (Table 3-19)

Inherited
■ Factor V Leiden (FVL) mutation:
  • Autosomal dominant mutation w/low penetrance
  • Causes activated protein C resistance (APCR); 90% of APCR is caused by FVL mutation
### TABLE 3-19  **Hypercoagulable Conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence in General Population (%)</th>
<th>Prevalence in Population with Thrombosis (%)</th>
<th>A/V Events</th>
<th>Relative Risk of Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVL mutation</td>
<td>5% of whites; rare in nonwhites</td>
<td>12%-40%</td>
<td>V</td>
<td>Heterozygous: 3-7 Homozygous: 80</td>
</tr>
<tr>
<td>Prothrombin G20210A mutation</td>
<td>3% of whites; rare in nonwhites</td>
<td>6%-18%</td>
<td>V</td>
<td>3</td>
</tr>
<tr>
<td>AT deficiency</td>
<td>0.02%</td>
<td>1%-3%</td>
<td>V</td>
<td>20-50</td>
</tr>
<tr>
<td>PC deficiency</td>
<td>0.2%-0.4%</td>
<td>3%-5%</td>
<td>V</td>
<td>7-15</td>
</tr>
<tr>
<td>PS deficiency</td>
<td>0.03%-0.1%</td>
<td>1%-5%</td>
<td>V</td>
<td>5-11</td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>1%-2%</td>
<td>5%-21%</td>
<td>V + A</td>
<td>2-11</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>5%-7%</td>
<td>10%</td>
<td>V + A</td>
<td>3</td>
</tr>
<tr>
<td>Elevated factor VIII level</td>
<td>11%</td>
<td>25%</td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

A, arterial; V, venous; FVL, factor V Leiden; AT, antithrombin; PC, protein C; PS, protein S.

- Most common genetic risk factor for venous thrombosis; accounts for thrombosis in 40%-50% of inherited cases
- OCP use in heterozygous carriers is associated with an 8-fold ↑ risk of thrombosis compared with noncarriers and a 35-fold ↑ risk of thrombosis compared with noncarriers not using OCP.
- Probably low risk of recurrent thrombotic events
- May be associated w/CVD in select high-risk subgroups

**Prothrombin G20210A mutation:**
- Autosomal dominant mutation w/↓ penetrance
- OCP use in heterozygous carriers is associated with a 16× ↑ risk of thrombosis compared with noncarriers not using OCP.
- Probably ↓ risk of recurrent thrombotic events
- May be associated w/CVD in select high-risk subgroups and young pts w/ischemic strokes

**Protein C, protein S, antithrombin deficiency:**
- Autosomal dominant inheritance; many mutations identified for each of these conditions
- ↓ Level or abnl function
- First episode of thrombosis usually in young adults
- ↑ Risk of recurrent thrombosis

**Protein C and protein S:**
- Lifetime risk of thromboembolic event up to 50%
- Homozygous condition very rare, usually associated w/lethal thrombosis in infancy
- Associated w/warfarin-induced skin necrosis, which occurs secondary to depletion of vitamin K-dependent anticoagulant factors sooner than procoagulant factors in the first few days of Rx

**Antithrombin deficiency:**
- Most thrombogenic of the identified inherited factors; lifetime risk of thromboembolic event up to 70%
- Homozygous condition very rare, probably not compatible w/ni fetal development
- Rarely, arterial thrombosis can occur
- Recurrent thrombotic events reported in up to 60% of pts
- Can cause heparin resistance

**Elevated factor VIII level:**
- May be an important risk factor for thrombosis in African American population
- ↑ Risk of recurrent thrombosis
- Genetic etiology suspected but not yet identified
Other possible causes: dysfibrinogenemias, ↑ thrombin activatable fibrinolysis inhibitor, plasminogen deficiency, ↑ factor IX and factor XI levels

Acquired

APS:
- Most common cause of acquired thrombophilia
- Can present as arterial or venous thrombosis, recurrent pregnancy loss, and adverse pregnancy outcomes
- Thromboembolic events occur in up to 30% of pts; high risk of recurrent thrombosis (up to 70% reported)
- See Antiphospholipid Antibody Syndrome for more information.

Hyperhomocysteinemia:
- Can be inherited (most commonly an autosomal recessive mutation in methylene tetrahydrofolate reductase gene) but more often secondary to poor dietary intake. Deficiency of folate, vitamin B₆, or vitamin B₁₂ accounts for ⅔ of cases.
- May be associated w/VTE, atherosclerotic disease (CV, cerebrovascular, and peripheral vascular), and possibly adverse pregnancy outcomes

Conditions associated w/↑ risk of thrombosis:
- Prior thrombosis
- Trauma
- Chronic medical illness: CHF, DM, obesity, nephrotic syndrome, IBD, PNH, HUS/ITP, DIC, sickle cell anemia
- Pregnancy (6x ↑ risk of thrombosis compared w/nonpregnant women), post partum, OCP (3-5x ↑ risk of thrombosis w/use, ↑ risk w/third-generation OCP), HRT (2x ↑ risk of thrombosis w/use), tamoxifen, raloxifene
- Immobilization, travel
- Surgery (especially orthopedic), central venous catheters
- Hyperviscosity syndromes
- Myeloproliferative disorders
- Malignancy: disease or treatment related
- HIT and thrombosis
- Cigarette smoking
- IV drug use

Treatment

Initial Rx is the same as for individuals w/o thrombophilia (exceptions for protein C and antithrombin deficiency).

Venous Thrombosis

UFH or LMWH followed by warfarin. Continue heparin for at least 5 days and until INR is therapeutic for 2 days; continue warfarin for at least 6 months. Aim for INR of 2-3. The intensity of anticoagulation is not affected by the presence of thrombophilia.

In pregnancy, full heparin anticoagulation during pregnancy and for at least 6 wk post partum. Minimum duration of anticoagulation is 6 mo.

Protein C Deficiency

Warfarin-induced skin necrosis: FFP or protein C concentrates until full anticoagulation w/heparin is achieved.

After full heparin anticoagulation, begin gradual warfarin loading (2 mg qd for 3 days and ↑ by 2-3 mg qd until target INR is reached). Continue heparin for 5-7 days until warfarin-induced anticoagulation is achieved.

Antithrombin Deficiency

Antithrombin concentrates may be used if there is difficulty achieving anticoagulation (heparin resistance), severe thrombosis, or recurrent thrombosis despite adequate anticoagulation.

Arterial Thrombosis

Anticoagulation and surgical consult for definitive procedure

Duration of Rx:
- Must consider risk and benefit; risk of major bleeding 2%-3% per yr in general population receiving anticoagulation but as high as 7%-9% per yr in the elderly. Long-term anticoagulation is usually not indicated given the low risk of recurrent thrombosis for most conditions and the bleeding risk associated w/anticoagulation.
Indefinite anticoagulation considered if ≥2 spontaneous thromboses or spontaneous thrombosis associated w/any of the following:
- Life-threatening thrombosis
- More than a single genetic defect
- Presence of antithrombin deficiency or antiphospholipid Abs

Clinical Pearls
- Consider screening family members: may be able to ↓ risk w/lifestyle modification and provide prophylaxis in high-risk situations.
- Previous episode of VTE is a major risk factor for recurrence regardless of the presence of thrombophilia. Risk is greatest in the first 2 yr after thrombosis. About 30% of all pts w/unprovoked VTE have recurrence within 10 yr. Risk of recurrence may be assessed by evaluation of residual thrombosis by Doppler U/S and w/D-dimer levels after completion of anticoagulation.
- Pts w/pregnancy-related complications may benefit from prophylaxis w/heparin and low-dose ASA.
- Genetic risk factors for thrombosis in nonwhites remain largely unknown.
- Interpreting w/u: many medical conditions cause acquired abnormalities.
- Heparin Rx: antithrombin levels ↓ by up to 50%, may affect testing of lupus anticoagulant and APC resistance assay.
- Warfarin Rx: protein C, protein S levels, and function ↓; antithrombin levels may ↑.
  - Antithrombin ↓ w/acute thrombosis (<10 days), surgery, liver disease, DIC, nephrotic syndrome, chemotherapy, estrogen Rx (HRT, OCP)
  - Protein S levels ↓ w/acute thrombosis (<10 days), surgery, liver disease, DIC, nephrotic syndrome, HIV infection, chemotherapy, pregnancy (free and total levels may be ↓ by 40%-60%), estrogen Rx (HRT, OCP)
  - Protein C ↓ w/acute thrombosis (<10 days), surgery, liver disease, chemotherapy, severe infection, and DIC. Levels ↑ w/age and hyperlipidemia.
  - APCR is ↑ w/pregnancy, estrogen Rx (HRT, OCP), and certain cancers. ↑ Factor VIII level and antiphospholipid Abs can cause APCR.

205 HYPERKALEMIA

Definition
Plasma potassium concentration >4.9 mEq/L.

Diagnosis (Fig. 3-27)
- R/o pseudohyperkalemia or lab error.
  - Repeat serum potassium level.
  - Obtain ECG; in pts w/suspected pseudohyperkalemia secondary to hemolized specimen or thrombocytosis, the ECG will not show any manifestations of hyperkalemia.
  - In pts w/thrombocytosis or severe leukocytosis, an accurate serum potassium level can be determined by drawing a heparinized sample.
- In pts w/true hyperkalemia and ECG or clinical manifestations, immediate intervention is indicated w/one or more measures, depending on the severity of hyperkalemia.
  - Check pH, correct acidosis (if present).
  - Check Ca, Mg, glucose, electrolytes, BUN, and Cr levels.
- Monitor ECG: ECG manifestations (Fig. 3-28)
  - Mild hyperkalemia: peaking or tenting of T waves, PVCs
  - Severe hyperkalemia: peaking of T waves, widening of QRS complex, depressed ST segments, prolongation of PR interval, sinus arrest, deep S wave, PVCs, VT, VF, and cardiac arrest

Etiology
- Pseudohyperkalemia
  - Hemolyzed specimen
  - Severe thrombocytosis (platelet count >10⁶ mL)
  - Severe leukocytosis (WBC >10⁶/mL)
  - Fist clenching during phlebotomy
**Figure 3-27.** Diagnostic algorithm for hyperkalemia.

**Figure 3-28.** The earliest change with hyperkalemia is peaking (“tenting”) of the T waves. With progressive increases in serum potassium, the QRS complexes widen, the P waves decrease in amplitude and may disappear; and finally, a sine wave pattern leads to asystole.

- ↑ Potassium intake (often in setting of impaired excretion)
  - Potassium replacement Rx
  - ↑ Potassium diet
  - Salt substitutes w/potassium
  - Potassium salts of abx
- ↓ Renal excretion
  - Potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride)
  - Renal insufficiency
  - Mineralocorticoid deficiency
  - Hyporeninemic hypoaldosteronism (DM)
  - Tubular unresponsiveness to aldosterone (e.g., SLE, MM, sickle cell disease)
HYPERMAGNESEMIA

- Type 4 RTA
- ACEIs
- Heparin administration
- NSAIDs
- TMP-SMZ
- β-Blockers
- Pentamidine

Redistribution (excessive cellular release)
- Acidemia (each 0.1 ↓ in pH ↑ the serum potassium by 0.4-0.6 mEq/L); lactic acidosis and ketoacidosis cause min. redistribution.
- Insulin deficiency
- Drugs (e.g., succinylcholine, markedly ↑ digitalis level, arginine, β-adrenergic blockers)
- Hypertonicity
- Hemolysis
- Tissue necrosis, rhabdo, burns
- Hyperkalemic periodic paralysis

Treatment Options
- Glucose, 50 g IV bolus or IV infusion of 500 mL of 10% dextrose solution, plus 10 U of regular insulin IV—onset of action is 30 min, duration 3 hr
- Ca gluconate (10% solution), 5-10 mL during 3 min—onset of action is <5 min, duration <1 hr
- Sodium polystyrene sulfonate (Kayexalate), PO or by NG tube: 20-50 g Kayexalate plus 100-200 mL of 20% sorbitol; retention enema: 50 g Kayexalate in 200 mL of water—onset of action 1-2 hr, duration 3 hr
- Sodium bicarbonate 1 ampule (44 mEq) during 5 min—onset of action 30 min, duration 3 hr
- Furosemide 40-160 mg IV during 30 min—onset of action at start of diuresis
- Dialysis (hemodialysis or peritoneal)—onset of action 5 min after start of dialysis

206 HYPERLIPIDEMIA

Definition
- Primary hyperlipoproteinemia refers to a group of genetic disorders of the lipid transport proteins in the blood, manifested as abnormally ↑ levels of cholesterol, TGs, or both in the serum of affected pts. Table 3-20 classifies lipid disorders.
- Secondary causes of hyperlipoproteinemias include
  - DM
  - Glycogen storage diseases
  - Lipodystrophies
  - Glucocorticoid use/excess
  - Alcohol
  - Oral contraceptives
  - Renal disease
  - Hepatic dysfunction

Treatment
- Guidelines for lipid management from the Adult Treatment Panel III (ATP III) are shown in Box 3-3.

207 HYPERMAGNESEMIA

Definition
Plasma Mg concentration >2.3 mg/dL.

Diagnosis
H&P
- Clinical manifestations: paresthesias, hypotension, confusion, ↓ DTRs, paralysis, coma, apnea; acute hypermagnesemia suppresses PTH secretion and can produce hypocalcemia.

ECG
- ECG manifestations: ↓ PR interval, heart block, peaked T waves, ↑ QRS duration
<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Plasma Lipid Levels</th>
<th>Genotype</th>
<th>Xanthomas</th>
<th>Other Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal or elevated</td>
<td>Elevated lipemia</td>
<td>Familial lipoprotein lipase deficiency, Apo CII deficiency</td>
<td>Eruptive, tuberoeruptive</td>
</tr>
<tr>
<td>II A</td>
<td>Normal aortic stenosis (homozygous FHC)</td>
<td>Elevated</td>
<td>FHC, familial combined hyperlipidemia—polygenic and sporadic hypercholesterolemia</td>
<td>Tendinous, xanthelasma, tuberous; planar (homozygous)</td>
</tr>
<tr>
<td>II B</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Familial combined hyperlipidemia, FHC</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Elevated</td>
<td>Elevated</td>
<td>Familial dysbetalipoproteinemia</td>
<td>Planar (especially palmar), tuberous</td>
</tr>
<tr>
<td>IV</td>
<td>Normal or elevated</td>
<td>Elevated symptoms, gallbladder disease</td>
<td>Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia</td>
<td>Usually none; rarely eruptive or tuberoeruptive</td>
</tr>
<tr>
<td>V</td>
<td>Normal or elevated</td>
<td>Elevated</td>
<td>Homozygous FHC</td>
<td>Eruptive, tuberoeruptive</td>
</tr>
</tbody>
</table>

Apo, apolipoprotein; FHC, familial hypercholesterolemia.
**ATP III Guidelines for Lipid Management**

**STEP 1.** Determine lipoprotein levels—obtain complete lipoprotein profile after 9- to 12-hr fast.

**ATP III classification of LDL, total, and HDL cholesterol (mg/dL):**

<table>
<thead>
<tr>
<th>Cholesterol</th>
<th>Primary Target of Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL Cholesterol</td>
<td>&lt;100 Optimal</td>
</tr>
<tr>
<td>100-129</td>
<td>Near optimal/above optimal</td>
</tr>
<tr>
<td>130-159</td>
<td>Borderline high</td>
</tr>
<tr>
<td>160-189</td>
<td>High</td>
</tr>
<tr>
<td>≥190</td>
<td>Very high</td>
</tr>
</tbody>
</table>

| Total Cholesterol |<200 Desirable |
| 200-239 |Borderline high |
| ≥240 |High |

| HDL Cholesterol |<40 Low |
| ≥60 |High |

**STEP 2.** Initiate therapeutic lifestyle changes (TLC) if LDL is above goal.

**TLC features:**
- TLC diet:
  - Saturated fat <7% of calories, cholesterol <200 mg/day
  - Consider ↑ viscous (soluble) fiber (10-25 g/day) and plant stanols/sterols (2 g/day) as therapeutic options to enhance LDL ↓
- Weight management
- ↑ Physical activity

**STEP 3.** Consider adding drug Rx to TLC:
- Simultaneously for CHD and CHD equivalents
- After 3 mo for other risk categories

**Drugs affecting lipoprotein metabolism:**

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Agents and Daily Doses</th>
<th>Lipid/ Lipoprotein Effects</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG CoA reductase inhibitors (statins)</td>
<td>Lovastatin (20-80 mg)</td>
<td>LDL ↓ 18%-55%</td>
<td>Myopathy ↑ Liver enzymes</td>
<td>Absolute: Active or chronic liver disease Relative: Concomitant use of certain drugs</td>
</tr>
<tr>
<td></td>
<td>Simvastatin (20-80 mg)</td>
<td>LDL ↓ 15%-30%</td>
<td>HDL ↑ 5%-15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pravastatin (20-40 mg)</td>
<td>LDL ↓ 15%-30%</td>
<td>HDL ↑ 5%-15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin (20-80 mg)</td>
<td>LDL ↓ 15%-30%</td>
<td>HDL ↑ 5%-15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Atorvastatin (10-80 mg)</td>
<td>LDL ↓ 15%-30%</td>
<td>HDL ↑ 5%-15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin (5-40 mg)</td>
<td>LDL ↓ 15%-30%</td>
<td>HDL ↑ 5%-15%</td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Cholestyramine (4-16 g)</td>
<td>LDL ↓ 15%-30%</td>
<td>GI distress Constipation ↓ Absorption of other drugs</td>
<td>Absolute: Dysbetalipoproteinemia Relative: TG &gt;400 mg/dL</td>
</tr>
<tr>
<td></td>
<td>Colestipol (5-20 g)</td>
<td>LDL ↓ 15%-30%</td>
<td>HDL ↑ 5%-15%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colesevelam (2.6-3.8 g)</td>
<td>LDL ↓ 15%-30%</td>
<td>HDL ↑ 5%-15%</td>
<td></td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Immediate-release (crystalline) nicotinic acid (1.5-3 g), extended-release nicotinic acid (Niaspan; 1-2 g), sustained-release nicotinic acid (1-2 g)</td>
<td>LDL ↓ 15%-30%</td>
<td>Flushing Hyperglycemia Hyperuricemia Upper GI distress Hepatotoxicity</td>
<td>Absolute: Chronic liver disease Relative: Diabetes Hyperuricemia PUD</td>
</tr>
</tbody>
</table>
### ATP III Guidelines for Lipid Management—cont’d

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Agents and Doses</th>
<th>Lipid/Lipoprotein Effects</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibric acids</td>
<td>Gemfibrozil (600 mg bid)</td>
<td>LDL ↓ 5%-20% (may be ↑ in pts w/high TG)</td>
<td>Dyspepsia</td>
<td>Absolute:</td>
</tr>
<tr>
<td></td>
<td>Fenofibrate (45-200 mg)</td>
<td>HDL ↑ 10%-20%</td>
<td>Gallstones</td>
<td>■ Severe renal disease</td>
</tr>
<tr>
<td></td>
<td>Clofibrate (1000 mg bid)</td>
<td>TG ↓ 20%-50%</td>
<td>Myopathy</td>
<td>■ Severe hepatic disease</td>
</tr>
</tbody>
</table>

#### STEP 4. Identify metabolic syndrome and treat, if present, after 3 mo of TLC. Clinical identification of the metabolic syndrome—any 3 of the following:

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd obesity</td>
<td>Waist circumference ↑</td>
</tr>
<tr>
<td>Men</td>
<td>&gt;102 cm (&gt;40 in)</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;88 cm (&gt;35 in)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>&lt;40 mg/dL</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;50 mg/dL</td>
</tr>
<tr>
<td>Women</td>
<td>Borderline high</td>
</tr>
<tr>
<td>BP</td>
<td>≥130/85 mm Hg</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>&gt;100 mg/dL</td>
</tr>
</tbody>
</table>

#### Treatment of the metabolic syndrome:
- Treat underlying causes (overweight/obesity and physical inactivity) by:
  - Intensifying weight management
  - ↑ Physical activity
- Treat lipid and nonlipid risk factors if they persist despite these lifestyle Rx by:
  - Treating HTN
  - Using ASA for CHD pts to ↓ prothrombotic state
  - Treating elevated triglycerides and/or low HDL (as shown in Step 5)

#### STEP 5. Treat elevated triglycerides and low HDL. ATP III classification of serum triglycerides (mg/dL):

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150</td>
<td>NI</td>
</tr>
<tr>
<td>150-199</td>
<td>Borderline high</td>
</tr>
<tr>
<td>200-499</td>
<td>High</td>
</tr>
<tr>
<td>&gt;500</td>
<td>Very high</td>
</tr>
</tbody>
</table>

#### Treatment of elevated triglycerides (≥150 mg/dL):
- Primary aim of Rx is to reach LDL goal
- Intensify weight management
- ↑ Physical activity
- If triglycerides are >200 mg/dL after LDL goal is reached, set secondary goal for non-HDL cholesterol (total − HDL) 30 mg/dL higher than LDL goal

#### Treatment of low HDL cholesterol (<40 mg/dL):
- First reach LDL goal, then:
  - Intensify weight management and ↑ physical activity
  - If triglycerides 200-499 mg/dL, achieve non-HDL goal
  - If triglycerides <200 mg/dL (isolated low HDL) in CHD or CHD equivalent, consider nicotinic acid or fibrate
  - If triglycerides elevated, consider fish oil supplement of 2-4 g/day

---

*Cyclosporine, macrolide abx, various antifungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used w/appropriate caution).

†Some male pts can develop multiple metabolic risk factors when the waist circumference is only marginally ↑, e.g., 94-102 cm (37-39 inches). Such pts may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similar to men w/categorical ↑ in waist circumference.
Chapter 3  Diseases and Disorders

**Etiology**
- Renal failure (↓ GFR)
- ↓ Renal excretion secondary to salt depletion
- Abuse of antacids and laxatives containing Mg in pts w/renal insufficiency
- Endocrinopathies (deficiency of mineralocorticoid or thyroid hormone)
- ↑ Tissue breakdown (rhabdo)
- Redistribution: DKA, pheochromocytoma
- Other: lithium, volume depletion, familial hypocalciuric hypercalcemia

**Treatment**
- Identify and correct underlying disorder.
- Intracardiac conduction abnormalities can be treated w/IV Ca gluconate.
- Dialysis for severe hypermagnesemia

**HYPERNATREMIA**

**Definition**
Plasma sodium concentration >144 mEq/L.

**Diagnosis**
**H&P**
- Clinical manifestations vary w/degree of hypernatremia and rapidity of onset; they range from confusion and lethargy to seizures and coma.

**Labs**
- Serum lytes, BUN, Cr, TSH, glucose

**Etiology** (Fig. 3-29)
- Isovolemic (↓ TBW, nl TBNa and ECF)
  - DI (neurogenic and nephrogenic)
  - Skin loss (hyperemia), iatrogenic, reset osmostat
- Hypervolemic (↑ TBW, ↑↑ TBNa and ECF)
  - Iatrogenic (administration of hypernatremic solutions)
  - Mineralocorticoid excess (Conn’s syndrome, Cushing’s syndrome)
  - Salt ingestion

**FIGURE 3-29.** Diagnostic algorithm for hypernatremia.
Hypovolemic: loss of H₂O and Na⁺ (H₂O loss >Na⁺)
- Renal losses (e.g., diuretics, glycosuria)
- GI, respiratory, skin losses
- Adrenal deficiencies

**Treatment**

- **Isovolemic hypernatremia**
  - Fluid replacement w/D₅W. Correct only half of estimated water deficit in initial 24 hr. The rate of correction of serum sodium should not exceed 1 mEq/L/hr in acute hypernatremia, 0.5 mEq/L/hr in chronic hypernatremia.
  - Calculate water deficit in hypernatremic pts
    \[
    \text{H₂O deficit in liters} = 0.6 \times \text{BW (kg)} \times \left( \frac{\text{measured Na}^+}{140} - 1 \right)
    \]

- **Hypovolemic hypernatremia**
  - Fluid replacement w/isotonic saline solution
  - The rate of correction of plasma osmolarity should not exceed 2 mOsm/kg/hr.

- **Hypervolemic hypernatremia**
  - Fluid replacement w/D₅W (to correct hypertonicity) is instituted after use of loop diuretics (to ↑ sodium excretion).

---

**209 HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)**

**Definition**
State of extreme hyperglycemia, marked dehydration, serum hyperosmolarity, ΔMS, and absence of ketoacidosis (Table 3-21).

**Diagnosis**

**H&P**
- Evidence of extreme dehydration (poor skin turgor, sunken eyeballs, dry mucous membranes)
- Neurologic defects (reversible hemiplegia, focal seizures)
- Orthostatic hypotension, tachycardia
- Evidence of precipitating factors (pneumonia, infected skin ulcer)
- Coma (25% of pts), delirium

**Labs**
- Hyperglycemia: serum glucose usually >600 mg/dL
- Hyperosmolality: serum osmolality usually >340 mOsm/L
- Serum sodium: may be ↓, nl, or ↑; if nl or ↑, the pt is severely dehydrated because ↑ glucose draws fluid from intracellular space, ↓ serum sodium; the corrected sodium can be obtained by ↑ the serum sodium

**TABLE 3-21 A Comparison of Diabetic Ketoacidosis (DKA) and Hyperosmolar Hyperglycemic State (HHS)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>Usually &lt;40 yr</td>
<td>Usually &gt;60 yr</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Usually &lt;2 days</td>
<td>Usually &gt;5 days</td>
</tr>
<tr>
<td>Serum glucose concentration</td>
<td>Usually &lt;800 mg/dL</td>
<td>Usually &gt;800 mg/dL</td>
</tr>
<tr>
<td>Serum sodium concentration (Na⁺)</td>
<td>More likely to be normal or low</td>
<td>More likely to be normal or high</td>
</tr>
<tr>
<td>Serum bicarbonate concentration</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>pH</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>Usually &lt;350 mOsm/kg</td>
<td>Usually &gt;350 mOsm/kg</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>Occasionally clinical symptoms</td>
<td>Rarely (never?) clinical</td>
</tr>
<tr>
<td>Prognosis</td>
<td>3%-10% mortality rate</td>
<td>10%-20% mortality rate</td>
</tr>
<tr>
<td>Subsequent course</td>
<td>Insulin therapy required in almost all cases</td>
<td>Insulin therapy not required in most cases</td>
</tr>
</tbody>
</table>

**Per Osm**

**Perglycemic STAT (hhs)**

**Table 3-21**

**Feature**

**DKA**

**HHS**

<table>
<thead>
<tr>
<th>Age of patient</th>
<th>Usually &lt;40 yr</th>
<th>Usually &gt;60 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of symptoms</td>
<td>Usually &lt;2 days</td>
<td>Usually &gt;5 days</td>
</tr>
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<td>Usually &gt;800 mg/dL</td>
</tr>
<tr>
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<td>More likely to be normal or low</td>
<td>More likely to be normal or high</td>
</tr>
<tr>
<td>Serum bicarbonate concentration</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>pH</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>Usually &lt;350 mOsm/kg</td>
<td>Usually &gt;350 mOsm/kg</td>
</tr>
<tr>
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<td>Rarely (never?) clinical</td>
</tr>
<tr>
<td>Prognosis</td>
<td>3%-10% mortality rate</td>
<td>10%-20% mortality rate</td>
</tr>
<tr>
<td>Subsequent course</td>
<td>Insulin therapy required in almost all cases</td>
<td>Insulin therapy not required in most cases</td>
</tr>
</tbody>
</table>

**Delta MS**

**ΔMS**

**Absence of ketoacidosis**

**Table 3-21**

**DKA**

**HHS**

<table>
<thead>
<tr>
<th>Feature</th>
<th>DKA</th>
<th>HHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient</td>
<td>Usually &lt;40 yr</td>
<td>Usually &gt;60 yr</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Usually &lt;2 days</td>
<td>Usually &gt;5 days</td>
</tr>
<tr>
<td>Serum glucose concentration</td>
<td>Usually &lt;800 mg/dL</td>
<td>Usually &gt;800 mg/dL</td>
</tr>
<tr>
<td>Serum sodium concentration (Na⁺)</td>
<td>More likely to be normal or low</td>
<td>More likely to be normal or high</td>
</tr>
<tr>
<td>Serum bicarbonate concentration</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td>pH</td>
<td>Low</td>
<td>Normal</td>
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<tr>
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<td>Insulin therapy required in almost all cases</td>
<td>Insulin therapy not required in most cases</td>
</tr>
</tbody>
</table>
Chapter 3  Diseases and Disorders

concentration by 1.6 mEq/dL for every 100 mg/dL ↑ in the serum glucose level above nl.
- Serum potassium: may be ↓, nl, or ↑; regardless of the initial serum level, the total body deficit is approximately 5-15 mEq/kg.
- Serum bicarbonate: usually >12 mEq/L (average is 17 mEq/L)
- Arterial pH: usually <7.2 (average is 7.26); both serum bicarbonate and arterial pH may be lower if lactic acidosis is present.
- BUN: azotemia (prerenal) is usually present (BUN generally ranges from 60-90 mg/dL).
- Phosphorus: hypophosphatemia (average deficit is 70-140 mM)
- Ca: hypocalcemia (average deficit is 50-100 mEq)
- Mg: hypomagnesemia (average deficit is 50-100 mEq)
- CBC w/diff, U/A, blood and urine cultures should be performed to r/o infectious etiology.

Etiology
- Infections, 20%-25% (e.g., pneumonia, UTI, sepsis)
- New or previously unrecognized diabetes (30%-50%)
- Reduction or omission of diabetic medication
- Stress (MI, CVA)
- Drugs: diuretics (dehydration), phenytoin, diazoxide (impaired insulin secretion)

Treatment
- Vigorous IV fluid replacement: the volume and rate of fluid replacement are determined by renal and cardiac function. Typically, infuse 1000-1500 mL/hr for the initial 1-2 L; then ↓ the rate of infusion to 500 mL/hr and monitor urinary output, blood chemistries, and BP; use 0.9% NS (isotonic solution) if the pt is hypotensive or serum osmolarity is <320 mOsm/L; otherwise use 0.45% NS solution. Slower infusion rate may be used initially in pts w/ compromised CV or renal status.
- Replace electrolytes and monitor serum levels frequently (e.g., serum sodium and potassium q2h for the first 12 hr). Serum KCl replacement in pts w/nl renal function and adequate urinary output is started when the serum potassium level is <5.2 mEq/L (e.g., 10 mEq KCl/hr if potassium level is 4-5.2 mEq/L). Continuous ECG monitoring and hourly measurement of urinary output are recommended.
- Correct hyperglycemia. The goal is for plasma glucose to decline by at least 75-100 mg/dL/hr.
  - Vigorous IV hydration will ↓ the serum glucose level in most pts by 80 mg/dL/hr; a regular insulin IV bolus (10 U) is often not necessary.
  - Low-dose insulin infusion at 1-2 U/hr (e.g., 25 U of regular insulin in 250 mL of 0.9% NS solution at 20 mL/hr) until the serum glucose level approaches 300 mg/dL; then the pt is started on regular SC insulin w/sliding scale coverage. If the plasma glucose does not ↓ during 2-4 hr despite adequate fluid administration and urine output, consider doubling the hourly insulin dose.
  - Glucose should be monitored 2h in the initial 12 hr.
  - Hypophosphatemia/hypomagnesemia in the absence of renal failure, phosphate can be administered at a rate of 0.1 mmol/kg/hr (5-10 mmol/hr) to a max of 80-120 mmol in 24 hr. Mg replacement, in absence of renal failure, can be administered IM (0.05-0.10 mL/kg of 20% Mg sulfate) or as IV infusion (4-8 mL of 20% Mg sulfate [0.08-0.16 mEq/kg]). Repeated Mg, phosphate, and Ca levels should be obtained after 12-24 hr.

Clinical Pearl
- The typical pt presenting w/hyperosmolar coma is an elderly or bed-confined diabetic w/impaired ability to communicate thirst who is evaluated after an interval of 1-2 wk of prolonged osmotic diuresis.

210 HYPERPARATHYROIDISM

Definition
Endocrine disorder caused by the excessive secretion of PTH from the parathyroid glands.
Diagnosis

H&P
- Exam may be entirely nl. The presence of signs and sx varies w/the rapidity of development and degree of hypercalcemia.

Labs
- ↑ Serum ionized Ca level, ↓ serum phosphorus, and nl/↑ alk phos
- ↑ Urine Ca level (in contrast w/↓↓ urinary Ca levels seen in pts w/familial hypocalciuric hypercalcemia)
- The serum PTH level is the single best test for initial evaluation of confirmed hypercalcemia. The “intact” PTH (iPTH) is the best assay. The iPTH distinguishes primary hyperparathyroidism from hypercalcemia caused by malignant disease when the serum Ca level is >12 mg/dL.

ECG
- ECG may reveal ↓ QT interval secondary to hypercalcemia.

Etiology
- A single adenoma is found in 80% of pts; 90% of the adenomas are found within one of the parathyroid glands, the other 10% are in ectopic sites (lateral neck, thyroid, mediastinum, retroesophagus).
- Parathyroid gland hyperplasia occurs in 20% of pts.
- Primary hyperthyroidism is associated w/MEN I and II.

Treatment
- Unless contraindicated, pts should maintain ↑ intake of fluids (3-5 L/day) and sodium chloride (>400 mEq/day) to ↑ renal Ca excretion. Ca intake should not be overly restricted because a ↓ Ca diet may ↑ PTH secretion. A moderate daily Ca intake of 800-1000 mg/day and vitamin D intake of 400 IU/day is reasonable.
- Potential hypercalcemic agents (e.g., thiazide diuretics) should be discontinued.
- Surgery is the only effective treatment of primary hyperparathyroidism. It is indicated in all pts younger than 50 yr and in pts w/complications from hyperthyroidism, such as nephrolithiasis and osteopenia. The conventional surgical approach is bilateral neck exploration under general anesthesia. Minimally invasive adenomectomy guided by preoperative technetium Tc 99m sestamibi scanning or U/S plus spiral CT is an alternative to conventional neck exploration. With the minimally invasive approach, the solitary adenoma is excised through a small unilateral incision w/the pt under local cervical block anesthesia.
- Percutaneous ethanol injection into the parathyroid gland should be considered in selected pts who have undergone a subtotal parathyroidectomy for multigland disease and have recurrent hyperparathyroidism as a result of remnant gland. Percutaneous alcohol ablation of the parathyroid gland may also be a suitable Rx for pts who are unwilling or unable to undergo parathyroidectomy.
- Asymptomatic elderly pts can be observed conservatively w/periodic monitoring of serum Ca level and review of sx. Serum Cr and PTH levels should also be obtained at 6- to 12-mo intervals, bone density (cortical and trabecular) yearly. Criteria for medical monitoring of pts w/asymptomatic primary hyperparathyroidism are as follows:
  - Serum Ca level only mildly ↑
  - Asymptomatic pt
  - Nil bone status (no osteoporosis)
  - Nil kidney function and no urolithiasis or nephrocalcinosis
  - No previous episode of life-threatening hypercalcemia
- Nearly 25% of asymptomatic pts develop indications for surgery during observation.

Acute General Rx
The treatment of choice for acute severe hypercalcemia (serum Ca >13 mg/dL) or symptomatic pts is hydration w/NS and immediate institution of biphosphonate Rx. There is no evidence to support the common practice of using furosemide for hypercalcemia of any cause. Treatment should be as follows:
Vigorous IV hydration w/NS. Use NS w/caution in pts w/cardiac or renal insufficiency to avoid fluid overload.

Bisphosphonates are effective agents. Zoledronate (4 mg IV over a 15-min period in a solution of 50 mL of NS or D<sub>2</sub>W) or pamidronate (60-90 mg IV infusion over a 2-hr period in a solution of 50-200 mL of saline or D<sub>2</sub>W) are both effective.

Cinacalcet is an oral calcimimetic agent that directly ↓ PTH levels by ↑ the Ca-sensing receptor to extracellular Ca. The ↓ in PTH is associated w/a concomitant ↓ in serum Ca levels. It is indicated in treatment of secondary hyperparathyroidism in pts w/chronic kidney disease on dialysis and hypercalcemia in parathyroid carcinoma. Initial dose is 30 mg PO qd.

### 211 HYPERPHOSPHATEMIA

**Definition**
Plasma phosphate concentration >5 mg/dL.

**Diagnosis**
- Serum electrolytes, BUN, Cr, glucose, Mg, Ca, CPK, LDH, CBC, serum lipids
- 24-hr urine phosphate

**Etiology**
- Excessive phosphate administration
  - ↑ Oral intake or IV administration
  - Laxatives containing phosphate (phosphate tablets, phosphate enemas)
- ↓ Renal phosphate excretion
  - Acute or chronic renal failure
  - Hypoparathyroidism or pseudohypoparathyroidism
  - Acromegaly, thyrotoxicosis
  - Bisphosphonate Rx
  - Tumor calcinosis
  - Sickle cell anemia
- Transcellular shift out of cells
  - Chemotherapy of lymphoma or leukemia, tumor lysis syndrome, hemolysis
  - Acidosis
  - Rhabdo, malignant hyperthermia
- Artifact: in vitro hemolysis
- Pseudohyperphosphatemia: hyperlipidemia, paraproteinemia, hyperbilirubinemia

**Treatment**
- Administration of Ca carbonate (1 g w/each meal, gradually ↑ to 8-12 g of Ca carbonate a day) to bind phosphate in the gut and to prevent its absorption
- Insulin and glucose infusion (to promote cell phosphate uptake); may be useful when a rapid ↓ in phosphate is needed
- Institution of hemodialysis when renal failure is present

### 212 HYPERSENSITIVITY PNEUMONITIS (HP)

**Definition**
Group of pulmonary diseases characterized by an immunologically induced inflammation of the lung parenchyma, which is due to intense or repeated inhalation of an organic agent or inorganic chemicals.

**Diagnosis**

**H&P**
Clinical presentation: varies according to frequency and intensity of antigen exposure
- **Acute**: fever, cough, and dyspnea 4-6 hr after an intense exposure, lasting 18-24 hr
- **Subacute**: insidious onset of productive cough, dyspnea on exertion, anorexia, and weight loss, usually from a heavy, sustained exposure
- **Chronic**: gradually progressive cough, dyspnea, malaise, and weight loss, usually from low-grade or recurrent exposure
Chapter 3  Diseases and Disorders

Hypersplenism

Labs
- Routine lab tests do not make the dx, but typically the ESR, CRP, and leukocyte count are ↑. The total IgG is elevated, and RF is often +. Peripheral eosinophil count and serum IgE are generally nl.
- PFTs: restrictive ventilatory patterns are typically seen. ↓ FEV₁, VC, diffusing capacity, and static compliance
- ABG: mild hypoxemia
- Serum precipitin test: sensitive but not specific for HP (asymptomatic pts may have IgG Abs in serum)

Imaging
- CXR: nonspecific; may be nl in early stage
  - Acute/subacute: bilateral interstitial and alveolar nodular infiltrates in a patchy or homogeneous distribution. Apices are often spared.
  - Chronic: diffuse reticulonodular infiltrates and fibrosis. Honeycombing may develop.
- HRCT: no pathognomonic features but demonstrates air space and interstitial patterns in the acute and subacute stage. The chronic stage reveals honeycombing and bronchiectasis.

Diagnostic Criteria
- Major criteria:
  - H/o sx compatible w/HP that appear to worsen within hours after antigen exposure
  - Confirmation of exposure to the offending agent by hx, investigation of the environment, serum precipitin test, or BAL Ab
  - Compatible changes on CXR or HRCT of the chest
  - BAL fluid lymphocytosis (if performed)
  - Compatible histologic changes by lung bx (if performed)
  - Positive natural challenge (reproduction of sx and laboratory abnormalities after exposure to the suspected environment) or controlled inhalation challenge
- Minor criteria:
  - Basilar crackles
  - ↓ Diffusion capacity
  - Arterial hypoxemia (either at rest or w/exercise)

Etiology
- Numerous environmental agents, often encountered in occupational settings
- Common sources of antigens: “moldy” hay, silage, grain, or vegetables; bird droppings or feathers; low-molecular-weight chemicals (i.e., isocyanates), pharmaceutical products

Treatment
- Prednisone 0.5-1 mg/kg usually during 1-2 wk, then tapered during 4 wk. Glucocorticoids accelerate initial lung recovery but may have no effect long term.

213 Hypersplenism

Definition
Syndrome characterized by splenomegaly, cytopenia (↓ of one or more of the peripheral cell lines), and compensatory hyperplastic bone marrow.

Diagnosis
Labs
- CBC w/diff: cytopenia, neutrophilia (infection)
- Peripheral smear: abnl cells (malignant neoplasm, RBC abnormalities), organisms (bacteria, malaria, babesiosis)
- Bone marrow bx: hematologic, infiltrative disorders, hyperplasia of cytopenia cell lines
- Tests to dx suspected cause of splenomegaly: LFT, hepatitis serology, HIV, RF, ANA, others
Chapter 3  Diseases and Disorders

NOTE: RBC mass may be used to assess severity of anemia. If considering splenectomy secondary to severe anemia, RBC mass measurement will differentiate true anemia (↓ in RBCs) from dilutional anemia (plasma volume expansion).

**Imaging**
- U/S to determine splenic size
- CT scan/MRI to obtain structural information; r/o cysts, tumors, infarcts

**Treatment**
- Treat underlying disease
- Splenectomy is considered if
  - Indicated for the management of the underlying cause
  - Persistent symptomatic disease (severe cytopenia) not responding to Rx
  - Necessary for dx

**Clinical Pearls**
- Thrombocytopenia in hypersplenism is rarely <20 × 10^9/L. Counts below this suggest other diagnosis for thrombocytopenia.
- Cytopenias are usually correctable w/splenectomy; cell counts return to nl within a few weeks.

**214 HYPERTENSION (HTN)**

**Definition**
The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of HBP (JNC 7) classification and approach to HTN are described in Boxes 3-4, 3-5, and 3-6 and Figure 3-30. Table 3-22 describes antihypertensive drugs in pregnancy.

<table>
<thead>
<tr>
<th>Classification of BP</th>
<th>SBP (mm Hg)</th>
<th>DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and</td>
</tr>
<tr>
<td>Pre-HTN</td>
<td>120-139</td>
<td>or</td>
</tr>
<tr>
<td>HTN, stage 1</td>
<td>140-159</td>
<td>or</td>
</tr>
<tr>
<td>HTN, stage 2</td>
<td>≥160</td>
<td>or</td>
</tr>
</tbody>
</table>

**Diagnostic w/u of HTN**
- Assess risk factors and comorbidities.
- Reveal identifiable causes of HTN.
- Assess presence of target organ damage.
- Conduct H&P.
- Obtain laboratory tests: U/A, blood glucose, Hct and lipid panel, serum potassium, Cr, and Ca. Optional: urinary alb/Cr ratio.
- Obtain ECG.

**Assess for Major CVD Risk Factors**
- HTN
- Obesity (BMI ≥30 kg/m²)
- Dyslipidemia
- DM
- Cigarette smoking

**Assess for Identifiable Causes of HTN**
- Sleep apnea
- Drug induced/related
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease

- Physical inactivity
- Microalbuminuria, estimated GFR <60 mL/min
- Age (>55 for men, >65 for women)
- FHx of premature CVD (men <55 yr, women <65 yr)
- Cushing’s syndrome or steroid Rx
- Pheochromocytoma
- Coarctation of aorta
- Thyroid/parathyroid disease
Box 3-5  •  HTN

BP Measurement Techniques

<table>
<thead>
<tr>
<th>Method</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-office</td>
<td>Two readings, 5 min apart, sitting in chair</td>
</tr>
<tr>
<td></td>
<td>Confirm elevated reading in contralateral arm.</td>
</tr>
<tr>
<td>Ambulatory BP monitoring</td>
<td>Indicated for evaluation of “white coat HTN”</td>
</tr>
<tr>
<td></td>
<td>Absence of 10%-20% BP ↓ during sleep may indicate ↑ CVD risk</td>
</tr>
<tr>
<td>Pt self-check</td>
<td>Provides information on response to Rx</td>
</tr>
<tr>
<td></td>
<td>May help improve adherence to Rx and is useful for evaluating</td>
</tr>
<tr>
<td></td>
<td>“white coat HTN”</td>
</tr>
</tbody>
</table>

Causes of Resistant HTN

- Improper BP measurement
- Excess sodium intake
- Inadequate diuretic Rx
- Medication
  - Inadequate doses
  - Drug actions and interaction (e.g., NSAIDs, illicit drugs, sympathomimetics, oral contraceptives)
  - OTC drugs and herbal supplements
- Excess alcohol intake
- Identifiable causes of HTN

Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Initial Rx Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Thiazide diuretic, β-blocker, ACEI, ARB, aldosterone</td>
</tr>
<tr>
<td></td>
<td>antagonist</td>
</tr>
<tr>
<td>Post MI</td>
<td>β-Blocker, ACEI, aldosterone antagonist</td>
</tr>
<tr>
<td>High CVD risk</td>
<td>Thiazide diuretic, β-blocker, ACEI, CCB</td>
</tr>
<tr>
<td>Diabetes</td>
<td>ACEI, β-blocker, ARB, CCB</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>prevention Thiazide diuretic, ACEI</td>
</tr>
</tbody>
</table>

Strategies for Improving Adherence to Rx

- Clinician empathy ↑ pt trust, motivation, and adherence to Rx
- Physicians should consider their pt’s cultural beliefs and individual attitudes in formulating Rx.

215 HYPERTENSIVE CRISIS

Definition

- Malignant HTN is a potentially life-threatening situation that is secondary to ↑ BP. The rate of BP ↑ is a critical factor. Clinical manifestations are grade IV hypertensive retinopathy (exudates, hemorrhages, and papilledema), CV or renal compromise, and encephalopathy. It requires immediate BP ↓ (not necessarily to nl ranges) to prevent or to limit target organ disease.
- Hypertensive emergencies are situations that require rapid (within 1 hr) ↓ of BP to avoid end-organ damage.
- Hypertensive urgencies are significant BP ↑ that should be corrected within 24 hr of presentation. They are not associated w/target organ damage; however, the risk of such damage is high.

Etiology

The most common causes of hypertensive emergencies and urgencies are as follows:

- Abrupt ↑ in BP in pts w/chronic HTN
- Withdrawal from antihypertensive agents (most commonly centrally acting agents and β agonists)
- Use of sympathomimetic agents (e.g., cocaine, phencyclidine, amphetamines)
**Box 3-6 • Lifestyle Modification for HTN**

**Principles of Lifestyle Modification**
- Encourage healthy lifestyles for all individuals.
- Prescribe lifestyle modifications for all pts w/pre-HTN and HTN.
- Components of lifestyle modifications include weight reduction, DASH eating plan, dietary sodium reduction, aerobic physical activity, and moderation of alcohol consumption.

**Lifestyle Modification Recommendations**

<table>
<thead>
<tr>
<th>Modifications</th>
<th>Recommendation</th>
<th>Average SBP Reduction Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain nl body weight (BMI 18.5-24.9 kg/m²)</td>
<td>5-20 mm Hg/10 kg</td>
</tr>
<tr>
<td>DASH eating plan</td>
<td>Adopt a diet rich in fruits, vegetables, and low-fat dairy products w/reduced content of saturated and total fat</td>
<td>8-14 mm Hg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to ≤100 mmol/day (2.4 g sodium or 6 g sodium chloride)</td>
<td>2-8 mm Hg</td>
</tr>
<tr>
<td>Aerobic physical activity</td>
<td>Regular aerobic physical activity (e.g., brisk walking) at least 30 min/day, most days of the week</td>
<td>4-9 mm Hg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Men: limit to ≤2 drinks/day</td>
<td>2-4 mm Hg</td>
</tr>
<tr>
<td></td>
<td>Women and lighter weight persons: limit to ≤1 drink/day</td>
<td></td>
</tr>
</tbody>
</table>

*Effects are dose and time dependent.

1 drink = $\frac{1}{2}$ oz or 15 mL ethanol (e.g., 12 oz beer, 5 oz wine, 1.5 oz 80-proof whiskey).

**TABLE 3-22 • Antihypertensive Drugs Used in Pregnancy**

<table>
<thead>
<tr>
<th>Suggested Drug</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central α-agonists</td>
<td>Methyldopa (C) is the drug of choice recommended by the NHBPEP Working Group</td>
</tr>
<tr>
<td>β-Blockers/α-blockers</td>
<td>Atenolol (C) and metoprolol (C) appear to be safe and effective in late pregnancy; labetalol hydrochloride (C) also appears to be effective (α- and β-blockers)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Potential synergism with magnesium sulfate may lead to precipitous hypotension (C)</td>
</tr>
<tr>
<td>ACEIs, angiotensin II receptor blockers</td>
<td>Fetal abnormalities, including death, can be caused, and these drugs should not be used in pregnancy (D)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Diuretics (C) are recommended for chronic HTN if prescribed before gestation or if pts appear to be salt sensitive; they are not recommended in cases of preeclampsia</td>
</tr>
<tr>
<td>Direct vasodilators</td>
<td>Hydralazine hydrochloride (C) is the parenteral drug of choice based on its long history of safety and efficacy</td>
</tr>
</tbody>
</table>

*There are several other antihypertensive drugs for which there are limited data. The U.S. Food and Drug Administration classifies pregnancy risk as follows: C, adverse effects in animals, no controlled trials in humans, use if risk appears justified; D, positive evidence of fetal risk.

*The report of the National High Blood Pressure Education Program (NHBPEP) Working Group on High Blood Pressure in Pregnancy permits continuation of drug therapy in women w/chronic HTN except for ACEIs. In addition, angiotensin II receptor blockers should not be used during pregnancy. In women w/ chronic HTN w/diastolic levels of 100 mm Hg or greater (lower when end-organ damage or underlying renal disease is present) and in women w/acute HTN when levels are 105 mm Hg or greater, these agents are suggested.
### PRINCIPLES OF HYPERTENSION TREATMENT

- Treat to BP <140/90 mmHg or BP <130/80 mmHg in pts with diabetes or chronic kidney disease.
- Majority of pts will require two medications to reach goal.

### ALGORITHM FOR TREATMENT OF HYPERTENSION

**LIFESTYLE MODIFICATIONS**

Not at goal BP (<140/90 mmHg) (≤130/80 mmHg for pts with diabetes or chronic kidney disease)

**INITIAL DRUG CHOICES**

**Stage 1 HTN** (SBP 140–159 or DBP 90–99 mmHg)
- Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination.

**Stage 2 HTN** (SBP ≥160 or DBP ≥100 mmHg)
- 2-drug combination for most (usually thiazide-type diuretic and ACEI, or ARB, or BB, or CCB).

**Drug(s) for the compelling indications**
- See Box 3–5, Compelling Indications for Individual Drug Classes
- Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.

**N**OT **A**T **G**OAL **BP**
- Optimize dosages or add additional drugs until goal BP is achieved. Consider consultation with HTN specialist.

**FIGURE 3-30.** Treatment of hypertension.

- Other: renovascular HTN, eclampsia, pheochromocytoma, coarctation of aorta, vasculitis, collagen-vascular disease, acute pyelonephritis, autonomic hyperactivity (e.g., spinal cord syndromes, GBS)

**Treatment**

Malignant HTN should be treated immediately. The choice of therapeutic agent varies w/the cause and manifestation of the hypertensive crisis. Table 3-23 lists medications commonly used in hypertensive emergencies. All of the drugs require close monitoring of the pt’s BP (preferably w/an A-line in an intensive care unit). A newer agent is clevidipine (Cleviprex), a CCB. Dosage is 1–2 mg/hr IV, doubling dose at 90-sec intervals PRN, then ↑ in smaller increments at longer intervals (5–10 min) up to (usual) 4–6 mg/hr or max 16 mg/hr. Onset of action is 2–4 min, duration 5–15 min. The following are three important points to consider in treating pts w/hypertensive emergencies:

- A plan for long-term Rx should be introduced at the time of initial emergency treatment.
- Agents that ↓ arterial pressure can cause the kidneys to retain sodium and water; therefore, the judicious administration of diuretics should accompany their use.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</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>Vasodilators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>0.25-10 µg/kg/min as IV infusion† (max dose for 10 min only)</td>
<td>Immediate</td>
<td>1-2 min</td>
<td>N/V, muscle twitching, sweating, thiocyanate and cyanide intoxication</td>
<td>Most hypertensive emergencies; caution w/high ICP or azotemia</td>
</tr>
<tr>
<td>Nicardipine hydrochloride</td>
<td>5-15 mg/hr IV</td>
<td>5-10 min</td>
<td>1-4 hr</td>
<td>Tachycardia, headache, flushing, local phlebitis</td>
<td>Most hypertensive emergencies except acute heart failure; caution w/ coronary ischemia</td>
</tr>
<tr>
<td>Fenoldopam mesylate</td>
<td>0.1-0.3 µg/kg/min IV infusion</td>
<td>&lt;5 min</td>
<td>30 min</td>
<td>Tachycardia, headache, nausea, flushing</td>
<td>Most hypertensive emergencies; caution w/glaucoma</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-100 µg/min as IV infusion†</td>
<td>2-5 min</td>
<td>3-5 min</td>
<td>Headache, vomiting, methemoglobinemia, tolerance w/ prolonged use</td>
<td>Coronary ischemia</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>1.25-5 mg q6h IV</td>
<td>15-30 min</td>
<td>6 hr</td>
<td>Precipitous fall in pressure in high-renin states; response variable</td>
<td>Acute left ventricular failure; avoid in acute MI</td>
</tr>
<tr>
<td>Hydralazine hydrochloride</td>
<td>10-20 mg IV; 10-50 mg IM</td>
<td>10-20 min to 30 min</td>
<td>3-8 hr</td>
<td>Tachycardia, flushing, headache, vomiting, aggravation of angina</td>
<td>Eclampsia</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>50-100 mg IV bolus repeated, or 15-30 mg/min infusion</td>
<td>2-4 min</td>
<td>6-12 hr</td>
<td>Nausea, flushing, tachycardia, chest pain</td>
<td>Now obsolete; when no intensive monitoring is available</td>
</tr>
<tr>
<td><strong>Adrenergic inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol hydrochloride</td>
<td>20-80 mg IV bolus q10min, 0.5-2.0 mg/min IV infusion</td>
<td>5-10 min</td>
<td>3-6 hr</td>
<td>Vomiting, scalp tingling, burning in throat, dizziness, nausea, heart block, orthostatic hypotension</td>
<td>Most hypertensive emergencies except acute heart failure</td>
</tr>
<tr>
<td>Esmolol hydrochloride</td>
<td>250-500 µg/kg/min for 1 min, then 50-100 µg/kg/min for 4 min; may repeat sequence</td>
<td>1-2 min</td>
<td>10-20 min</td>
<td>Hypotension, nausea</td>
<td>Aortic dissection; perioperative</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>5-15 mg IV</td>
<td>1-2 min</td>
<td>3-10 min</td>
<td>Tachycardia, flushing, headache</td>
<td>Catecholamine excess</td>
</tr>
</tbody>
</table>

*Hypotension may occur with all agents.
†Requires special delivery system.
The initial goal of antihypertensive Rx is not to achieve a normal BP but rather to gradually reduce the BP. With exception of pts w/aortic dissection, the initial goal in hypertensive emergencies is to ↓ the MAP by 25% within 2 hr and diastolic pressure to <100 mm Hg within 2-6 hr.

Hypertensive urgencies can be effectively treated w/the following oral agents:
- Clonidine 0.2 mg PO loading, then 0.1 mg every 20 min (to a max of 0.8 mg) until diastolic BP is ↓ ≥20 mm or below 110 mm Hg. Sedation, dry mouth, and dizziness are common side effects.
- Labetalol 200-300 mg single PO dose followed by 100-200 mg q8h. Onset of action is 60-120 min; duration is 12-24 hr. Bradycardia is a major side effect.

**HYPERTHYROIDISM**

**Definition**
Hypermetabolic state resulting from excess thyroid hormone.

**Diagnosis**

*H&P*
- Pts w/hyperthyroidism generally present w/the following clinical manifestations: tachycardia, tremor, hyperreflexia, anxiety, irritability, emotional lability, panic attacks, heat intolerance, sweating, ↑ appetite, diarrhea, weight loss, menstrual dysfunction (oligomenorrhea, amenorrhea). The presentation may be different in elderly pts (see later).
- Pts w/Graves’ disease may present w/exophthalmos, lid retraction, lid lag (Graves’ ophthalmopathy). The following signs and sx of ophthalmopathy may be present: blurring of vision, photophobia, ↑ lacrimation, double vision, deep orbital pressure. Clubbing of fingers associated w/periosteal new bone formation in other skeletal areas (Graves’ acropachy) and pretibial myxedema may also be noted.

**Labs** (*Fig. 3-31*)
- ↑ Free thyroxine (T₄)
- ↑ Free triiodothyronine (T₃): generally not necessary for dx

**FIGURE 3-31.** Diagnostic algorithm for hyperthyroidism.
Diseases or renin-angiotensin

- Renin levels
- Hyperreninemic
- Identify
- Levels ↓ in
- range
- renin-dependent, nlnl
- identify
- cases
dosteronism
- nl
- identify
- 24-hr RAIU is useful to distinguish hyperthyroidism from iatrogenic thyroid hormone synthesis (thyrotoxicosis factitia) and from thyroiditis
- An overactive thyroid shows ↑ uptake, whereas iatrogenic thyroid ingestion and painless or subacute thyroiditis show nl or ↓ uptake.
- The RAIU results also vary w/the etiology of the hyperthyroidism:
  - Graves’ disease: ↑ homogeneous uptake
  - Multinodular goiter: ↑ heterogeneous uptake
  - Hot nodule: single focus of ↑ uptake

Etiology

- Graves’ disease (diffuse toxic goiter): 80%-90% of all cases of hyperthyroidism
- Toxic multinodular goiter (Plummer’s disease)
- Toxic adenoma
- Iatrogenic and factitious
- Transient hyperthyroidism (subacute thyroiditis, Hashimoto’s thyroiditis)
- Rare causes: hypersecretion of TSH (e.g., pituitary neoplasms), struma ovarii, ingestion of large amount of iodine in a pt w/preexisting thyroid hyperplasia or adenoma (Jod-Basedow phenomenon), hydatidiform mole, carcinoma of thyroid, amiodarone Rx

Treatment

- Antithyroid drugs (thionamides): methimazole (Tapazole) inhibits thyroid hormone synthesis by blocking production of thyroid peroxidase.
- Adjunctive Rx to alleviate β-adrenergic sx of hyperthyroidism involves propranolol 20-40 mg PO q6h; dosage is gradually ↑ until sx are controlled.
- RAI is the treatment of choice for pts >21 yr of age and younger pts who have not achieved remission after 1 yr of antithyroid drug Rx.
- Subtotal thyroidectomy: indicated in obstructing goiters, in any pt who refuses RAI and cannot be adequately managed w/antithyroid medications (e.g., pts w/toxic adenoma or toxic multinodular goiter), and in pregnant pts who cannot be adequately managed w/antithyroid medication or develop side effects to them.

Clinical Pearl

- Elderly hyperthyroid pts may have only subtle signs (weight loss, tachycardia, fine skin, brittle nails). This form is known as apathetic hyperthyroidism and is manifested w/lethargy rather than with hyperkinetic activity. An enlarged thyroid gland may be absent. Coexisting medical disorders (most commonly cardiac disease) may also mask the sx. These pts often have unexplained CHF or new-onset AF.

217 HYPOALDOSTERONISM

Definition

Aldosterone deficiency or impaired aldosterone function.

Diagnosis

Labs

- ↑ Potassium, nl or ↓ sodium
- Hyperchloremic metabolic acidosis (caused by the absence of hydrogen-secreting action of aldosterone)
- ↑ BUN and Cr (secondary to renal disease)
- Hyperglycemia (DM is common in these pts)

Workup

Measurement of PRA after 4 hr of upright posture can differentiate hyporeninemic from hyperreninemic causes. Renin levels in the nl or ↓ range identify cases that are renin-angiotensin dependent, whereas ↑ renin levels identify cases that are renin-angiotensin independent. The dx and etiology of hypoaldosteronism can be confirmed w/the renin-aldosterone stimulation test:
Diseases and Disorders

**Chapter 3**

- Hyporeninemic hypoaldosteronism: low stimulated renin and aldosterone levels
- End-organ refractoriness to aldosterone action: high stimulated renin and aldosterone levels
- Adrenal gland abnormality: ↑ stimulated renin and ↓ aldosterone levels

**Etiology**
- Hyporeninemic hypoaldosteronism (renin-angiotensin dependent): ↓ aldosterone production secondary to ↓ renin production; the typical pt has renal disease secondary to various factors (e.g., DM, interstitial nephritis, MM).
- Hyperreninemic hypoaldosteronism (renin-angiotensin independent): renin production by the kidneys is intact; the defect is in aldosterone biosynthesis or in the action of angiotensin II. Common causes of this form of hypoaldosteronism are medications (ACEIs, heparin), lead poisoning, aldosterone enzyme defects, and severe illness.

**Treatment**
- ↓ Potassium diet w/liberal sodium intake (at least 4 g of sodium chloride per day)
- Avoidance of ACEIs and potassium-sparing diuretics
- Judicious use of fludrocortisone (0.05-0.1 mg PO q AM) in pts w/aldosterone deficiency associated w/deficiency of adrenal glucocorticoid hormones
- Furosemide 20-40 mg qd to correct hyperkalemia of hyporeninemic hypoaldosteronism

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**HYPOCALCEMIA**

**Definition**
Plasma Ca level <8.8 mg/dL.

**Diagnosis**

**H&P**
- Neuromuscular irritability
  - *Chvostek’s sign*: facial twitch after a gentle tapping over the facial nerve (can occur in 10%-25% of nl adults)
  - *Trousseau’s sign*: carpopedal spasm after inflation of BP cuff above the pt’s systolic BP for a 2- to 3-min duration
- Tetany, paresthesias, myopathy, seizures, muscle spasm or weakness
- Psychiatric disturbances: psychosis, depression, impaired cognitive function
- Soft tissue calcifications, ocular cataracts
- CV: arrhythmias, CHF (caused by ↓ myocardial contractility), ↑ QT interval, hypotension

**Labs** (Table 3-24, Fig. 3-32)
- Serum alb: to r/o hypoalbuminemia
- BUN, Cr: to r/o renal failure
- Serum Mg: to r/o severe hypomagnesemia
- Serum PO₄³⁻, alk phos: to differentiate hypoparathyroidism from vitamin D deficiency
- Serum PTH level by radioimmunoassay should be ordered only if the dx is uncertain w/the preceding tests.
  - ↑↑ PTH: pseudohypoparathyroidism
  - ↑ PTH: vitamin D deficiency
  - ↓ PTH: hypoparathyroidism

**Etiology**
- Renal insufficiency: hypocalcemia caused by
  - ↑ Ca deposits in bone and soft tissue secondary to ↑ serum PO₄³⁻ level
  - ↓ Production of 1,25-dihydroxyvitamin D
  - ↑ Loss of 25-OHD (nephrotic syndrome)
- Hypoalbuminemia: each ↓ in serum alb (g/L) will ↓ serum Ca by 0.8 mg/dL but will not change free (ionized) Ca
<table>
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<th>Urine Tests</th>
<th>Comments</th>
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<tr>
<td></td>
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<tr>
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<td>Type II</td>
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cAMP, cyclic adenosine monophosphate; [OH]D, hydroxycholecalciferol D; OH₂D, dihydroxycholecalciferol; PO₄, phosphate, PTH, parathormone; TmP, renal threshold for phosphorus.
**FIGURE 3-32.** Diagnostic algorithm for hypocalcemia.

- **Vitamin D deficiency**
  - Malabsorption (most common cause)
  - Inadequate intake
  - ↓ Production of 1,25-dihydroxyvitamin D (vitamin D–dependent rickets, renal failure)
  - ↓ Production of 25-OHD (parenchymal liver disease)
  - ↑ 25-OHD catabolism (phenytoin, phenobarbital)
  - End-organ resistance to 1,25-dihydroxyvitamin D
- **Hypomagnesemia:** hypocalcemia caused by
  - ↓ PTH secretion
  - Inhibition of PTH effect on bone
- **Pancreatitis, hyperphosphatemia, osteoblastic mets:** hypocalcemia is secondary to ↑ Ca deposits (bone, abd)
- **Pseudohypoparathyroidism:** autosomal recessive disorder characterized by short stature, shortening of metacarpal bones, obesity, and mental retardation; the hypocalcemia is secondary to congenital end-organ resistance to PTH
- Idiopathic hypoparathyroidism, surgical removal of parathyroids (e.g., neck surgery)
- **Hungry bones syndrome:** rapid transfer of Ca from plasma into bones after removal of a parathyroid tumor
- Sepsis
- Massive blood transfusion (as a result of EDTA in blood)

**Treatment**
- Acute, severe symptomatic hypocalcemia caused by hypoparathyroidism or vitamin D deficiency: give a slow IV bolus (over 15 min) of 10-30 mL of a 10% Ca gluconate solution followed by an infusion of 4 g Ca gluconate in 500 mL D5W over 4 hr (1 g Ca gluconate = 10 mL 10% Ca gluconate).
- **Hypoalbuminemia**
  - Improve nutritional status.
  - Ca replacement is not indicated because the free (ionized) Ca is nl.
Hypomagnesemia: correct the Mg deficiency
  • Severe hypomagnesemia (serum Mg level <0.8 mEq/L): give 1 g (8 mEq) of a 10% Mg sulfate solution IV slowly (during 15 min).
  • Moderate to severe hypomagnesemia (serum Mg level 0.8-1.3 mEq/L): give one 2-mL ampule of a 50% Mg solution IM; may repeat q4-6h.

Chronic hypocalcemia caused by hypoparathyroidism or vitamin D deficiency
  • Ca supplementation: 1-4 g/day of elemental Ca (e.g., Ca carbonate, 650 mg PO qid, will provide 1 g of elemental Ca/day).
  • Vitamin D replacement (e.g., calcitriol, 0.25 µg/day)

Chronic hypocalcemia caused by renal failure
  • Reduction of hyperphosphatemia w/phosphate-binding antacids
  • Vitamin D and oral Ca supplementation (as noted earlier)

219 HYPOGLYCEMIA

Definition
Hypoglycemia can be arbitrarily defined as a plasma glucose level <50 mg/dL. To establish the dx, the following 3 criteria are necessary:

■ Presence of sx
  • Adrenergic: sweating, anxiety, tremors, tachycardia, palpitations
  • Neuroglycopenic: seizures, fatigue, syncope, headache, behavior changes, visual disturbances, hemiplegia

■ ↓ Plasma glucose level in symptomatic pt
■ Relief of sx after ingestion of carbohydrates

Diagnosis

■ In a nl pt, when the plasma glucose level is ↓ (e.g., fasting state), the plasma insulin level is also ↓. Any pt presenting w/fasting hypoglycemia of unexplained cause should have the following tests drawn during the hypoglycemic episode (Table 3-25):
  • Plasma insulin level and proinsulin level
  • C-peptide (connecting peptide)
  • Plasma and urine sulfonylurea levels

Factitious hypoglycemia should be considered, especially if the pt has ready access to insulin or sulfonylureas (e.g., medical or paramedical personnel, family members who are diabetic or in the medical profession)
  • To dx factitious hypoglycemia secondary to sulfonylureas, screen serum and urine to determine the presence of sulfonylureas.
  • To dx factitious hypoglycemia secondary to insulin, the following tests may be obtained:
    • Insulin level, which is ↑↑ after exogenous insulin injection; proinsulin level, however, is ↓.
    • C-peptide: levels are ↑ in pts w/insulinoma and sulfonylureas but not after exogenous insulin injection.

Pancreatic islet cell neoplasms (insulinomas) are usually small (<3 cm), single, insulin-5–producing adenomas. Measurement of inappropriately ↑ serum insulin levels despite ↓ plasma glucose level after prolonged fasting (24–72 hr) is pathognomonic of these neoplasms.

The insulinoma can be located by selective pancreatic arteriography and removed surgically.

| TABLE 3-25 | Laboratory Differentiation of Factitious Hypoglycemia and Insulinoma |
|--------------------------|--------------------------|--------------------------|--------------------------|
| **Laboratory Test** | **Insulinoma** | **Exogenous Insulin** | **Sulfonylurea** |
| Plasma insulin level | ↑ | ↑↑ | ↑ |
| Insulin Ab(s) | None* | Present* | None* |
| Plasma/urine sulfonylurea levels | Absent | Absent | Present |
| C-peptide | ↑ | N/↓ | ↑ |

*May be present if the pt has had previous insulin injections (pork or beef insulin); will be absent if human insulin is given.
Etiology
- Reactive hypoglycemia
  - Hypoglycemia usually occurs 2-4 hr after a meal rich in carbohydrates.
  - These pts never have sx in the fasting state and rarely experience loss of consciousness secondary to their hypoglycemia.
  - Pts who have had subtotal gastrectomy rapidly absorb carbohydrates, causing an early ↑↑ plasma glucose level followed by a late insulin surge that reaches its peak when most of the glucose has been absorbed and that results in hypoglycemia.
- Type 2 (non–insulin-dependent) diabetics can experience hypoglycemia 3-4 hr postprandially secondary to a delayed and prolonged second phase of insulin secretion.
- Congenital deficiencies of enzymes necessary for carbohydrate metabolism and functional (idiopathic) hypoglycemia are additional causes of reactive hypoglycemia.
- Fasting hypoglycemia
  - Sx usually appear in the absence of food intake (at night or during early morning).
  - Etiology: insulinoma, mesenchymal tumors that synthesize insulin-like hormones, adrenal failure, glycogen storage disorders, severe liver disease or renal disease
- Iatrogenic or drug-induced: hypoglycemic drugs, excessive insulin replacement, factitious, ethanol-induced hypoglycemia

Treatment
- Variable, depending on etiology of hypoglycemia

220 HYPOKALEMIA

Definition
Plasma potassium concentration <3.3 mEq/L.

Diagnosis
- Distinguish true potassium depletion from redistribution (e.g., alkalosis, insulin administration) (Fig. 3-33).
- If the cause of hypokalemia is not apparent (e.g. diuretics, vomiting), measure 24-hr urinary potassium excretion while pt is receiving a regular dietary sodium intake.
  - <20 mEq: consider extrarenal potassium loss
  - >20 mEq: renal potassium loss
- If renal potassium wasting is suspected, the following steps are indicated:
  - Measure 24-hr urine chloride.
    - >10 mEq: diuretics, Bartter’s syndrome, mineralocorticoid excess (chloride unresponsive)
    - <10 mEq: vomiting, gastric drainage (chloride responsive)
  - Measure BP; if ↑, consider mineralocorticoid excess.
  - Measure serum HCO₃⁻: a ↓ level is suggestive of RTA.
- ECG manifestations (Fig. 3-34)
  - Mild hypokalemia: flattening of T waves, ST-segment depression, PVCs, ↑ QT interval
  - Severe hypokalemia: prominent U waves, AV conduction disturbances, VT, VF

Etiology
- Cellular shift (redistribution) and undetermined mechanisms
  - Alkalosis (each 0.1 ↑ in pH ↓ serum potassium by 0.4-0.6 mEq/L)
  - Insulin administration
  - Vitamin B₁₂ Rx for megaloblastic anemias, acute leukemias
  - Hypokalemic periodic paralysis: rare familial disorder manifested by recurrent attacks of flaccid paralysis and hypokalemia
  - β₂ Agonists, decongestants, bronchodilators, theophylline, caffeine
  - Barium poisoning, toluene intoxication, verapamil intoxication, chloroquine intoxication
  - Correction of digoxin intoxication w/digoxin Ab fragments (Digibind)
HYPOKALEMIA

- Renal excretion
  - Drugs: diuretics, including carbonic anhydrase inhibitors (e.g., acetazolamide); amphotericin B; high-dose sodium PCN, nafcillin, ampicillin, or carbenicillin; cisplatin, AGs, corticosteroids, mineralocorticoids, foscarnet sodium
  - RTA: distal (type 1) or proximal (type 2)

- R/o medication-induced (e.g., diuretics, β agonists, theophylline), prolonged diarrhea, vomiting

- 24-hr urine potassium excretion
  - >20 mEq/day
  - <20 mEq/day

- Renal potassium loss
  - Extrarenal potassium loss (diarrhea, vomiting, GI fistula, profuse sweating)

- Bartter's syndrome, diuretics, magnesium deficiency

- Primary aldosteronism

- Cushing's syndrome, mineralocorticoid ingestion

- Plasma aldosterone

- Plasma renin

- Renovascular HTN, renin-secreting tumor

Figure 3-33. Diagnostic algorithm for hypokalemia.
Chapter 3  Diseases and Disorders

HYPOMAGNESEMIA

Definition
Plasma Mg concentration <1.8 mg/dL.

Diagnosis
H&P
Clinical and laboratory manifestations
- Neuromuscular: weakness, hyperreflexia, fasciculations, tremors, convulsions, delirium, coma
- CV: cardiac arrhythmias
- Hypokalemia refractory to potassium replacement
- Hypocalcemia refractory to Ca replacement

Treatment
- PO potassium replacement is preferred
- IV infusion should generally not exceed 20 mEq/hr
- Monitor ECG and urinary output.
- Identify underlying cause and treat accordingly.
- IV NS solution in chloride-responsive hypokalemia

FIGURE 3-34. Variable ECG patterns can be seen with hypokalemia, ranging from slight T wave flattening to the appearance of prominent U waves, sometimes with ST depressions or T wave inversions. These patterns are not always directly related to the specific level of serum potassium.

- DKA, ureteroenterostomy
- Mg deficiency
- Postobstruction diuresis, diuretic phase of ATN
- Osmotic diuresis (e.g., mannitol)
- Bartter’s syndrome: hyperplasia of juxtaglomerular cells leading to ↑ renin and aldosterone, metabolic alkalosis, hypokalemia, muscle weakness, and tetany (seen in young adults)
- ↑ Mineralocorticoid activity (primary or secondary aldosteronism), Cushing’s syndrome
- Chronic metabolic alkalosis from loss of gastric fluid (↑ renal potassium secretion)
- GI loss
  - Vomiting, NG suction
  - Diarrhea
  - Laxative abuse
  - Villous adenoma
  - Fistulas
- Inadequate dietary intake (e.g., anorexia nervosa)
- Cutaneous loss (excessive sweating)
- High dietary sodium intake, excessive use of licorice
Labs
- Serum Mg, phosphorus, Ca, electrolytes, BUN, Cr, glucose
- 24-hr urine Mg, Cr
- ECG manifestations: prolonged QT interval, T wave flattening, prolonged PR interval, AF, torsades de pointes

Etiology
- GI and nutritional
  - Defective GI absorption (malabsorption)
  - Inadequate dietary intake (e.g., alcoholics)
  - Parenteral Rx w/o Mg
  - Chronic diarrhea, villous adenoma, prolonged NG suction, fistulas (small bowel, biliary)
- Excessive renal losses
  - Diuretics
  - RTA
  - Diuretic phase of ATN
  - Endocrine disturbances (DKA, hyperaldosteronism, hyperthyroidism, hyperparathyroidism), SIADH, Bartter’s syndrome, hypercalciuria, hypokalemia
  - Cisplatin, alcohol, cyclosporine, digoxin, pentamidine, mannitol, amphotericin B, foscarnet, MTX
- Redistribution: hypoalbuminemia, cirrhosis, administration of insulin and glucose, theophylline, epinephrine, acute pancreatitis, cardiopulmonary bypass
- Miscellaneous: sweating, burns, prolonged exercise, lactation, “hungry bones” syndrome

Treatment
- Correct Mg deficiency
  - Mild: 600 mg oxide PO provides 35 mEq of Mg; dosage is 1-2 tablets qd.
  - Moderate: 50% solution Mg sulfate (each 2-mL ampule contains 8 mEq or 96 mg of elemental Mg); dosage is one 2-mL ampule of 50% Mg solution q6h PRN.
  - Severe (serum Mg level <1 mg/dL) and symptomatic pt (seizures, tetany): 2 g Mg in 20 mL D5W IV during 60 min; monitor ECG, BP, pulse, respiration, DTRs, and urinary output. An alternative regimen is the administration of 6 g Mg sulfate (49 mEq) in 1000 mL of D5W during 3 hr, followed by 10 g of Mg sulfate in 2000 mL of 5% dextrose in water during 24 hr.
- Identify and correct underlying disorder.

HYponatREMIA

Definition
Plasma sodium concentration <134 mEq/L.

Diagnosis
- Serum electrolytes, BUN, Cr, glucose, uric acid, serum osmolality, TSH (Fig. 3-35)
- Urine sodium, urine osmolality

Etiology
Isovolemic
- SIADH
- Water intoxication (e.g., schizophrenic pts, primary polydipsia, sodium-free irrigant solutions, multiple tap-water enemas, dilute infant formulas). These entities are rare and often associated w/a deranged ADH axis.
- Renal failure
- Reset osmostat (e.g., chronic active TB, carcinomatosis)
- Glucocorticoid deficiency (hypopituitarism)
- Hypothyroidism
- Thiazide diuretics, NSAIDs, carbamazepine, amitriptyline, thioridazine, vincristine, cyclophosphamide, colchicine, tolbutamide, chlorpropamide, ACEIs, clofibrate, oxytocin, SSRIs, amiodarone
### Diseases and Disorders

#### Hyponatremia

**Serum osmolality**
- Normal
  - BUN, Cr, uric acid, urine osmolality, urinary sodium
- Isotonic hyponatremia
  - R/o hypothyroidism, hypopituitarism
- Hypertonic hyponatremia
  - R/o hyperglycemia, hypertonic infusions

**R/o secondary to renal failure**
- Significant ↑ of BUN, Cr

**R/o water intoxication**
- BUN, Cr, uric acid, variable urine osmolality

**R/o reset osmostat**
- Normal BUN, Cr, uric acid, variable urine osmolality

**R/o SIADH**
- ↓/normal BUN, Cr, urine osmolality, ↑ uric acid, ↓ urinary sodium

**R/o thiazide diuretic-induced hyponatremia**
- TSH, serum cortisol
- R/o SIADH
- R/o hypothyroidism, hypopituitarism
- R/o thiazide diuretic-induced hyponatremia (especially in elderly pts)

**Diagnostic algorithm for hyponatremia.**

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**Hypovolemic**
- Renal losses (diuretics, partial urinary tract obstruction, salt-losing renal disease)
- Extrarenal losses: GI (vomiting, diarrhea), extensive burns, third spacing (peritonitis, pancreatitis)
- Adrenal insufficiency

**Hypervolemic**
- CHF
- Nephrotic syndrome
- Cirrhosis
- Pregnancy
- Isotonic hyponatremia (nl serum osmolality)
- Pseudohyponatremia (↑ serum lipids and serum proteins). Newer sodium assays eliminate this problem.
- Isotonic infusion (e.g., glucose, mannitol)
- Hypertonic hyponatremia (↑ serum osmolality)
- Hyperglycemia: each 100 mg/dL ↑ in blood glucose level above nl ↓ plasma sodium concentration by 1.6 mEq/L
- Hypertonic infusions (e.g., glucose, mannitol)
**Treatment**

- **Isovolemic hyponatremia**
  - SIADH: fluid restriction unless acutely symptomatic
  - Acute symptomatic pt: hypertonic 3%-5% saline solution infusion; give 200-500 mL slowly, followed by fluid restriction to 750 mL/day for 24-48 hr. Hypertonic saline can be combined w/furosemide to limit treatment-induced expansion of the ECF volume.

- **Hypovolemic hyponatremia**: 0.9% NS infusion

- **Hypervolemic hyponatremia**: sodium and water restriction. The combination of captopril and furosemide is effective in pts w/hyponatremia resulting from CHF.

- **Chronic hyponatremia**: correction of chronic hyponatremia should be kept at a rate <10 mEq/L (mmol/L) in any 24-hr period to prevent myelinolysis, a neurologic disorder that can occur after rapid correction of hyponatremia. Initially named central pontine myelinolysis, this disease is now known to also affect extrapontine brain areas. Manifestations of myelinolysis usually evolve several days after correction of hyponatremia. Typical features are disorders of UMN, spastic quadriparesis and pseudobulbar palsy, and mental disorders ranging from mild confusion to coma. Death may occur. The motor and localizing signs of myelinolysis differ from the generalized encephalopathy that is caused by untreated hyponatremia.

**Clinical Pearls**

- In general, the serum sodium should be corrected only halfway to nl in the initial 24 hr (but not >1 mEq/L/hr) to prevent complications from rapid correction (cerebral edema, myelinolysis, seizures). A slower correction rate is indicated in pts w/chronic hyponatremia.

- In symptomatic pts w/hyponatremia, an ↑ in the serum sodium concentration of 2 mEq/L/hr to a level of 120-130 mEq/L is considered safe by some experts; however, less rapid correction may be indicated in pts w/severe or chronic hyponatremia.

**HYPOPHOSPHATEMIA**

**Definition**

Plasma phosphate concentration <2.5 mg/dL.

**Diagnosis**

- Serum phosphate, Ca, glucose, electrolytes, BUN, Cr
- 24-hr urine phosphate, Cr

**Etiology**

- ↓ Intake (prolonged starvation, alcoholics, hyperalimentation, or IV infusion w/o phosphorus)
- Malabsorption
- Phosphate-binding antacid
- Renal loss
  - RTA
  - Fanconi syndrome, vitamin D–resistant rickets
  - ATN (diuretic phase)
  - Hyperparathyroidism (primary or secondary)
  - Familial hypophosphatemia
  - Hypokalemia, hypomagnesemia
  - Acute volume expansion
  - Glycosuria, idiopathic hypercalciuria
  - Acetazolamide
- Transcellular shift into cells
  - Alcohol withdrawal
  - DKA (recovery phase)
  - Glucose-insulin or catecholamine infusion
  - Anabolic steroids
  - TPN
  - Theophylline OD
• Severe hyperthermia; recovery from hypothermia
• “Hungry bones” syndrome

Treatment
- Mild to moderate hypophosphatemia (>1 mg/dL): Neutra-Phos capsules (250 mg per capsule), 2 capsules tid.
- Severe symptomatic hypophosphatemia (<1 mg/dL): IV administration of phosphate salts (0.08-0.16 mmol/kg during 6 hr) repeated q6h until serum phosphate level is >1.5 mg/dL.

HYPOPITUITARISM

Definition
Partial or complete loss of secretion of one or more pituitary hormones resulting from diseases of the hypothalamus or pituitary gland.

Diagnosis

H&P
The onset of hypopituitarism is usually gradual, and sx are related to the lack of one or more hormones or mass effect if a pituitary tumor is the cause. Specific sx depend on the hormones involved, the severity of the deficiencies, and the pt’s age at onset.

- Mass effect of a pituitary tumor can cause headaches and visual field disturbances.
- Corticotropin deficiency:
  - Fatigue and weakness, no appetite, abd pain, N/V
  - Hypotension, hair loss, and ΔMS
- Thyrotropin deficiency:
  - Fatigue and weakness, weight gain, cold intolerance, and constipation
  - Bradycardia, hung-up reflexes, pretibial edema, and hair loss
- Gonadotropin deficiency:
  - Loss of libido, erectile dysfunction, amenorrhea, hot flashes, dyspareunia, infertility
  - Gynecomastia w/lack of hair growth and ↓ muscle mass
- GH deficiency:
  - Growth retardation in children
  - Easy fatigue, hypoglycemia
  - ↓ Muscle mass and obesity
- Hyperprolactinemia
  - Galactorrhea
  - Hypogonadism
- Vasopressin deficiency:
  - Polyuria, polydipsia, and nocturia
  - Hypotension and dehydration

Labs
- Corticotropin deficiency:
  - Serum AM cortisol level usually ↓ (<3 g/dL)
  - Corticotropin stimulation test using 250 µg of corticotropin given IV and measuring serum cortisol before and 30 and 60 min after administration. Abnormal response is an ↑ in serum cortisol level >20 µg/dL.
  - With pituitary disease, these tests may be indeterminate, and more dynamic testing, such as an insulin tolerance or metyrapone test, may be necessary.
- Thyrotropin deficiency:
  - TSH and free T4 measurements
  - Primary hypothyroidism: ↑ TSH w/↓ free T4
  - Secondary hypothyroidism: nl/↑ TSH, ↓ free T4, and ↓ T3RU
- Gonadotropin deficiency:
  - FSH, LH, estrogen, and testosterone measurements
  - In men, hypogonadotropic hypogonadism occurs w/↓ testosterone levels and nl/↓ FSH and LH levels.
  - In premenopausal women w/amenorrhea, ↓ estrogen w/nl/↓ FSH and LH levels is typically seen.
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- GH deficiency:
  - Insulin-induced hypoglycemia stimulation test using 0.1-0.15 unit/kg regular insulin given IV and measuring GH 30, 60, and 120 min after administration. Abnormal response is a GH level >10 µg/dL.
  - Serum IGF-1 can also be measured after provocative testing.
- Hyperprolactinemia: prolactin levels ↑ in prolactin-secreting pituitary adenomas
- Vasopressin deficiency:
  - U/A: ↓ specific gravity
  - ↓ Urine osmo
  - ↑ Serum osmo
  - Fluid deprivation test during 18 hr w/inability to concentrate the urine
  - ↓ Serum vasopressin
  - Electrolytes may show hyponatremia and exclude hyperglycemia.

**Imaging**
- MRI of pituitary

**Etiology**
Hypopituitarism is the result of destruction of pituitary cells caused by
- Pituitary tumors
  - Macroadenomas >10 mm
  - Microadenomas <10 mm
- Pituitary apoplexy caused by hemorrhage or infarction of the pituitary gland
- Pituitary radiation Rx
- Pituitary surgery
- *Empty sella syndrome* w/enlargement of the sella turcica and flattening of the pituitary gland caused by extension of the subarachnoid space and filling of CSF into the sella turcica
- Infiltrative disease including sarcoidosis, hemochromatosis, histiocytosis X, Wegener’s granulomatosis, and lymphocytic hypophysitis
- Infection (TB, mycosis, and syphilis)
- Head trauma
- Internal carotid artery aneurysm

**Treatment**
- Hormone replacement Rx and surgery, irradiation, or medications in pts w/pituitary tumors
- Acute situations like adrenal crisis and myxedema coma are discussed separately.
- **Chronic Rx**: Treatment is lifelong and requires the following hormone replacement Rx:
  - ACTH deficiency: hydrocortisone 20 mg PO q AM and 10 mg PO q PM or prednisone 5 mg PO q AM and 2.5 mg PO q PM. Dexamethasone or prednisone is often preferred because of longer duration of action.
  - LH and FSH deficiency:
    - In men, testosterone replacement IM q2-3wk or transdermal.
    - In women who are not interested in fertility, conjugated estrogen 0.3-1.25 mg/day and held the last 5-7 days of each month w/the addition of medroxyprogesterone 10 mg/day given during days 15-25 of the nl menstrual cycle. In those who have secondary hypogonadism and wish to become pregnant, pulsatile GnRH may be of benefit.
  - TSH deficiency: levothyroxine 0.05-0.15 mg/day
  - GH deficiency: GH is generally not used in adults; however, it can be given at 0.04-0.08 mg/kg/day SC in children.
  - ADH deficiency: desmopressin (DDAVP) 10-20 µg by intranasal spray or 0.05-0.1 mg PO bid is used in pts w/DI.

**HYPOOTHERMIA**

**Definition**
Rectal temperature <35°C (95.8°F). *Accidental hypothermia* is unintentionally induced ↓ in core temperature in absence of preoptic anterior hypothalamic conditions.
Hypothermia

Diagnosis

H&P
- The clinical presentation varies with the severity of hypothermia; shivering may be absent if body temperature is <33.3°C (92°F) or in pts taking phenothiazines.
- Hypothermia may masquerade as CVA, ataxia, or slurred speech, or the pt may appear comatose or clinically dead.
- Physiologic stages of hypothermia:
  - Mild hypothermia (32.2°C-35°C [90°F-95°F]): arrhythmias, ataxia
  - Moderate hypothermia (28°C-32.2°C [82.4°F-90°F]): progressive ↓ of level of consciousness, pulse, CO, and respiration; fibrillation, dysrhythmias (↑ susceptibility to VT); elimination of shivering mechanism for thermogenesis
  - Severe hypothermia (<28°C [82.4°F]): absence of reflexes or response to pain, ↓ cerebral blood flow, ↓ CO₂, ↑ risk of ventricular fibrillation or asystole

Labs
- Metabolic and respiratory acidosis are usually present. ↓ K⁺ initially, then ↑ K⁺ w/↓ temp; extreme hyperkalemia indicates a poor prognosis; ↓ Hct (caused by hemoconcentration), ↓ leukocytes, ↓ platelets (caused by splenic sequestration), ↑ clotting time

Imaging
- CXR: generally not helpful; may reveal evidence of aspiration (e.g., intoxicated pt w/aspiration pneumonia)
- ECG (Fig. 3-56): ↑ PR, QT, and QRS segments; ↑ ST segments, inverted T waves, AV block; hypothermic J waves (Osborn waves), characterized by notching of the junction of the QRS complex and ST segments, may appear at 25°C-30°C.

Treatment
- Secure an airway before warming all unconscious pts; precede endotracheal intubation w/oxygenation (if possible) to ↓ the risk of arrhythmias during the procedure.
- Peripheral vasoconstriction may impede placement of a peripheral IV catheter; consider femoral venous access as an alternative to the jugular or subclavian sites to avoid ventricular stimulation.
- A Foley catheter should be inserted, and urinary output should be monitored and maintained >0.5-1 mL/kg/hr w/intravascular volume replacement.
- Continuous ECG monitoring of pts is recommended; consider ventricular arrhythmias Rx w/bretylium; lidocaine is generally ineffective, and procaainamide is associated w/↑ incidence of VF in hypothermic pts.
- Correct severe acidosis and electrolyte abnormalities.
- Hypothyroidism, if present, should be promptly treated (refer to Myxedema Coma).
- If clinical evidence suggests adrenal insufficiency, administer IV methylprednisolone.
- In pts unresponsive to verbal or noxious stimuli or w/ΔMS, 100 mg of thiamine, 0.4 mg of naloxone, and 1 ampule of 50% dextrose may be given.
Warm (104°F-113°F [40°C-45°C]), humidified oxygen should also be given if it is available.

Specific treatment:
- Mild hypothermia (rectal temperature <32.3°C [90°F]): passive external rewarming is indicated. Place the pt in a warm room (temperature >21°C [69.8°F]) and cover w/insulating material after gently removing wet clothing; recommended rewarming rates vary between 0.5°C and 20°C/hr but should not exceed 0.55°C/hr in elderly pts.
- Moderate to severe hypothermia: delivery of heat through fluids: warm GI irrigation (w/saline enemas and by NG tube); IV fluids (usually D5NS w/o potassium) warmed to 104°F-107.6°F (40°C-42°C), peritoneal dialysis w/dialysate heated to 40.5°C-42.5°C, inhalation of heated humidified oxygen. Consider immersion in a bath of warm water (40°C-41°C); active external rewarming may produce shock because of excessive peripheral vasodilation. Ideal candidates are previously healthy, young pts w/acute immersion hypothermia. Extracorporeal blood warming w/cardiopulmonary bypass appears to be an efficacious rewarming technique in young, otherwise healthy pts.

**226 HYPOTHYROIDISM**

**Definition**
Disorder caused by the inadequate secretion of thyroid hormone.

**Diagnosis**

**H&P**
- Skin: dry, coarse, thick, cool, sallow (yellow color caused by carotenemia); nonpitting edema in skin of eyelids and hands (myxedema) secondary to infiltration of SC tissues by a hydrophilic mucopolysaccharide substance
- Hair: brittle and coarse; loss of outer third of eyebrows
- Facies: dulled expression, thickened tongue, thick slow-moving lips
- Thyroid gland: may or may not be palpable (depending on the cause of the hypothyroidism)
- Heart sounds: distant, possible pericardial effusion
- Pulse: bradycardia
- Neurologic: delayed relaxation phase of the DTRs, cerebellar ataxia, hearing impairment, poor memory, peripheral neuropathies w/paresthesia
- Musculoskeletal: carpal tunnel syndrome, muscle stiffness, weakness

**Labs** (Fig. 3-37, Table 3-26)
- ↑ TSH: TSH may be nl if pt has secondary or tertiary hypothyroidism, pt is receiving dopamine or corticosteroids, or the level is obtained after severe illness.
- ↓ Free T₄
- Other common laboratory abnormalities: hyperlipidemia, hyponatremia, and anemia
- ↑ Antimicrosomal and antithyroglobulin Ab titers: useful only when autoimmune thyroiditis is suspected as the cause of the hypothyroidism

**Etiology**
- Primary hypothyroidism (thyroid gland dysfunction): cause of >90% of the cases of hypothyroidism
  - Hashimoto’s thyroiditis: most common cause of hypothyroidism after 8 yr of age
  - Idiopathic myxedema (nongoitrous form of Hashimoto’s thyroiditis)
  - Previous treatment of hyperthyroidism (radioiodine Rx, subtotal thyroidectomy)
  - Subacute thyroiditis
  - Radiation Rx to the neck (usually for malignant disease)
  - Iodine deficiency or excess
  - Drugs (lithium, PAS, sulfonamides, phenylbutazone, amiodarone, thiourea)
  - Congenital (approximately 1 case per 4000 live births)
  - Prolonged treatment w/iodides
HYPOTHYROIDISM

Secondary hypothyroidism:
- pituitary dysfunction, postpartum necrosis, neoplasm, infiltrative disease causing deficiency of TSH
- Tertiary hypothyroidism: hypothalamic disease (granuloma, neoplasm, or irradiation causing deficiency of TRH)
- Tissue resistance to thyroid hormone: rare

Treatment
- Start replacement Rx w/levothyroxine 25-100 µg/day, depending on pt’s age and severity of the disease. The dose may be ↑ every 6-8 wk, depending on the clinical response and serum TSH level. Elderly pts and pts w/CAD should be started w/12.5-25 µg/day (higher doses may precipitate angina).

TABLE 3-26  Findings in Thyroid Function Tests in Various Clinical Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>T₄</th>
<th>FT₄ I</th>
<th>T₃</th>
<th>FT₃ I</th>
<th>TSH</th>
<th>TSI</th>
<th>TRH Stimulation</th>
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<tr>
<td><strong>Hyperthyroidism</strong></td>
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<tr>
<td>Graves’ disease</td>
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<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>+, −</td>
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<tr>
<td>Toxic nodular goiter</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Pituitary</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>TSH-secreting tumors</td>
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<td></td>
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<td></td>
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<tr>
<td>T₃ thyrotoxicosis</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>†, −</td>
<td>−</td>
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<tr>
<td>T₄ thyrotoxicosis</td>
<td>↑</td>
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<td>N</td>
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<tr>
<td><strong>Hypothyroidism</strong></td>
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<tr>
<td>Primary</td>
<td>↓</td>
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<tr>
<td>Secondary</td>
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<td>↓, N</td>
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<tr>
<td>Tertiary</td>
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<td>↓, N</td>
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<td>N</td>
</tr>
<tr>
<td>Peripheral unresponsiveness</td>
<td>↑, N</td>
<td>↑, N</td>
<td>↑,</td>
<td>N</td>
<td>↑,</td>
<td>N −</td>
<td>N, ↑</td>
</tr>
</tbody>
</table>

†, −, variable; FT₃I, free T₃ index; FT₄I, free T₄ index; T₃, triiodothyronine; T₄, thyroxine; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin.
Clinical Pearls
- Periodic monitoring of TSH level is an essential part of treatment. Pts should be evaluated w/office visit and TSH levels every 6-8 wk until the pt is clinically euthyroid and the TSH level is normalized.
- For monitoring Rx in pts w/central hypothyroidism, measurement of serum free thyroxine (free T₄ level) is appropriate; it should be maintained in the upper half of the nl range.
- Pregnant pts also have ↑ requirements. Women w/hypothyroidism should ↑ their levothyroxine dose by approximately 30% as soon as pregnancy is confirmed and have frequent testing.

IDIOPATHIC PULMONARY FIBROSIS (IPF)
Definition
Specific form of chronic fibrosing interstitial pneumonia w/ histopathologic features characteristic of usual interstitial pneumonia. Disease characterized by progressive parenchymal scarring and loss of pulmonary function.

Diagnosis
H&P
- Gradual onset (>6 mo) of exertional dyspnea and nonproductive cough
- Tachypnea to compensate for stiff noncompliant lung
- Fine bibasilar inspiratory crackles (in >80% of pts)
- Clubbing (25%-50% of pts)

PFTs
- Restrictive impairment (↓ VC and TLC); obstructive picture seen only in smokers w/IPF; ↓ DLCO

Labs
- Mild anemia; ↑ ESR, LDH, CRP; low-titer ANA seen in up to 30% of pts
- Limited role for bronchioalveolar lavage either in dx or monitoring of IPF
- Gold standard for dx is lung bx (open thoracotomy or video-assisted thoracoscopy). Hallmark features: heterogeneous distribution of parenchymal fibrosis against background of mild inflammation (usual interstitial pneumonia).

Imaging
- CXR: bilateral reticular opacities most prominent in the periphery and lower lobes. Peripheral honeycombing may be seen.
- HRCT: patchy peripheral reticular abnormalities w/intralobular linear opacities, irregular septal thickening, subpleural honeycombing, and ground-glass appearance

Treatment
- No proven treatment of IPF and little evidence to support the routine use of any specific Rx
- Conventional Rx includes a trial of corticosteroids at 0.5 mg/kg × 4 wk, 0.25 mg/kg × 8 wk, then tapered down in combination w/azathioprine or cyclophosphamide for 3-6 mo; 10%-30% of pts may respond.
- Rx is continued for up to 24 mo if the pt improves or is stable. Long-term treatment only w/objective evidence of continued improvement or stabilization.
- Single-lung or bilateral lung transplantation is the only Rx shown to prolong survival in IPF. Post-transplantation 5-year survival for IPF pts → 40%.
- Treatment agents designed to target the fibrotic process include N-acetylcysteine, pirfenidone, interferon gamma-1b, coumadin, and etanercept. These are under investigation and show some initial promise.

IGA NEPHROPATHY
Definition
Proliferative GN associated w/predominant deposition of IgA in the mesangium.

Diagnosis
H&P
- Two common presentations are (1) recurrent macroscopic hematuria often associated w/URI and (2) persistent microscopic hematuria.
Physical findings are usually unremarkable except HTN (20%-30% of pts w/chronic disease) and edema (5% of pts w/nephrotic-range proteinuria).

**Labs**
- Renal bx: restricted to pts w/sustained proteinuria >1 g/day or worsening renal function
- U/A: protein, RBC, WBC, and RBC casts
- ↑ Serum Cr
- 24-hr urine for proteinuria and Cr
- ↑ Serum IgA (50% of pts). It has no clinical utility.

**Etiology**
- Most cases: idiopathic/primary
- Secondary associations: hepatitis B, alcoholic cirrhosis, celiac disease, IBD, psoriasis, sarcoidosis, cystic fibrosis, cancer of lungs/larynx/pancreas, HIV, SLE, RA, diabetic nephropathy, SS, Reiter’s syndrome

**Treatment**
- HTN: ACEIs. Goal BP is <125/75 in presence of proteinuria >1 g/day.
- Persistent proteinuria >1 g/day: ACEIs or ARB ± steroids
- Severe renal disease or crescentic, RPGN: steroid and cyclophosphamide combination for the first 2 mo, followed by steroids and azathioprine for 2 yr for maintenance Rx
- Tonsillectomy: if bouts of recurrent macroscopic hematuria are associated w/tonsillitis
- ESRD: kidney transplantation
- Dyslipidemia: statins
- Role of mycophenolate and plasmapheresis: controversial

**Clinical Pearl**
- IgA nephropathy seems to be a kidney-restricted form of Henoch-Schönlein purpura.

### IMMUNE THROMBOCYTOPENIC PURPURA (ITP)

**Definition**
Autoimmune disorder in which Ab-coated or immune complex–coated platelets are destroyed prematurely by the reticuloendothelial system, resulting in peripheral thrombocytopenia.

**Diagnosis**
**H&P**
- Children: generally present w/sudden onset of bruising and petechiae from severe thrombocytopenia
- Adults: insidious presentation; dx often made on incidental routine labs
- Exam may be entirely nl.
- Petechiae, purpura, epistaxis, or heme-positive stool from GI bleeding in pts w/severe thrombocytopenia

**Labs**
- CBC, platelet count, and peripheral smear: platelets are ↓ but nl in size
- Direct assay for platelet-bound Ab (+ predictive value 80%-83%)
- Additional labs: HIV, ANA, TSH, LFTs, bone marrow exam

**Imaging**
- CT of abd in pts w/splenomegaly (r/o lymphoma)

**Etiology**
- Drugs commonly implicated: quinidine, heparin, abx (linezolid, vancomycin, sulfonamides, rifampin), platelet inhibitors (tirofiban, abciximab, epifibatide), cimetidine, NSAIDs, thiazide diuretics, antirheumatic agents (gold salts, penicillamine), acetaminophen, and chemotherapeutic agents (cyclosporine, fludarabine, oxaliplatin)

**Treatment**
- Asymptomatic pts w/platelets >30,000/mm³: observation
- Pts w/neurologic sx, internal bleeding, or those undergoing emergency surgery: methylprednisolone 30 mg/kg/day IV plus IVIG (1 g/kg/day for 2-3 days) and infusion of platelets
Diseases to secondary generally i

Staphylococcus aureus or infection skin

Inflammatory Definition

Superficial Definition

H&P Diagnosis

Streptococcus Treatment

PO 2% Bullous

Nonbullous

Common >

Eltrombopag

Rituximab: Platelet

Splenectomy: adults w/platelets >20,000/mm^3 after 6 wk of medical treatment or after 6 mo if >20 mg of prednisone/day is required to maintain platelets >30,000/mm^3. In children, splenectomy is reserved for persistent thrombocytopenia (>1 yr) and clinically significant bleeding.

Platelet transfusion: only in case of life-threatening hemorrhage

Rituximab: useful in ITP resistant to conventional treatment

Eltrombopag and romiplostim: Rx of chronic ITP refractory to corticosteroids, immunoglobulins, or splenectomy

Clinical Pearls

>80% of children have a complete remission within 8 wk.

In adults, the course of the disease is chronic, and only 5% of adults have spontaneous remission.

The principal cause of death from ITP is ICH (1% of children, 5% of adults).

230 IMPETIGO

Definition

Superficial skin infection generally secondary to Staphylococcus aureus or Streptococcus spp.

Diagnosis

Common presentations are bullous impetigo (due to staph) and nonbullous impetigo (due to strep).

Nonbullous impetigo: starts as single red macule or papule that quickly becomes a vesicle. Rupture of the vesicle produces an erosion, the contents of which dry to form honey-colored crusts. Multiple lesions w/golden yellow crusts and weeping areas found on the skin around the nose, mouth, and limbs.

Bullous impetigo: presence of vesicles that enlarge rapidly to form bullae w/contents that vary from clear to cloudy. Subsequent collapse of the center of the bullae; the peripheral areas may retain fluid, and a honey-colored crust may appear in the center; as the lesions enlarge and become contiguous w/the others, a scaling border replaces the fluid-filled rim; there is min. erythema surrounding the lesions.

Etiology

S. aureus coagulase + is the dominant microorganism. The bullous form is caused by an epidermolytic toxin produced at the site of infection.

S. pyogenes (group A beta-hemolytic streptococci): M-T serotypes of this organism associated w/acute nephritis are 2, 49, 55, 57, and 60.

Treatment

2% mupirocin ointment tid × 10 days or retapamulin 1% applied bid × 5 days to the affected area or until all lesions have cleared

PO abx in severe cases: dicloxacillin 250 mg qid × 7-10 days; cephalaxin 250 mg qid × 7-10 days; azithromycin 500 mg on day 1, 250 mg on days 2-5

231 INCLUSION BODY MYOSITIS

Definition

Inflammatory myopathy.

Diagnosis

H&P

Steadily progressive asymmetric and painless muscle weakness and atrophy of the finger or wrist flexors (commonly the flexor pollicis longus), knee extensor (quadriceps), and foot dorsiflexion. Over time, weakness spreads to involve other muscles.
Diseases of muscle fiber most (PM), breakdown. The (DM), inflammation and dermatomyositis are caused by atrophic quadriceps muscles.

Facial and neck weakness can be seen. Early loss of patellar reflexes

**Labs**
- TSH
- ANA, RF, ds-DNA, ESR, Scl-70, anti-Ro, and anti-La to r/o other autoimmune diseases
- CPK (nl to ↑ 3-5× nl)
- Muscle bx: small angular atrophic and denervated fibers. CD8 cytotoxic T-cell endomysial infiltration. Intracytoplasmic rimmed vacuoles and cytoplasmic tubofilamentous inclusions on electron microscopic examination of the affected muscle fiber.

**EMG**
- Active myopathic changes (fibrillation potentials, positive sharp waves, and short-duration, low-amplitude, polyphasic motor unit action potentials). Mixed myopathic and neurogenic changes can also be seen.

**Treatment**
- Corticosteroids, cyclophosphamide, chlorambucil, azathioprine, cyclosporine, MTX, anabolic steroid oxandrolone, and IVIG have been used but w/o evidence of significant benefit.
- Interferon beta-1a at 30 and 60 mg IM/wk regimens did not result in significant improvement in muscle strength or muscle mass.
- Oxandrolone (a synthetic anabolic steroid) may ↑ muscle strength, but further studies are needed.
- Botulinum toxin A injection into upper esophageal sphincter

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### INFLAMMATORY MYOPATHIES (POLYMYOSITIS, DERMATOMYOSITIS)

**Definition**
Idiopathic diseases of muscle characterized clinically by muscle weakness and pathologically by inflammation and muscle fiber breakdown. The 3 most common are dermatomyositis (DM), polymyositis (PM), and inclusion body myositis.

**Diagnosis**

**H&P**
- Most pts have a subacute onset, during weeks to months.
- Symmetric proximal muscle weakness involving the neck flexors, shoulder, and pelvic girdles
- Difficulty getting up from a chair, climbing stairs, reaching for objects above head, or combing hair
- Sensation and reflexes are preserved.
- Dysphagia and dysphonia result from pharyngeal muscle involvement.
- Esophageal dysmotility often occurs in DM.
- Respiratory failure from associated pulmonary fibrosis
- Cardiac conduction abnormalities can be seen w/DM.
- Systemic autoimmune disease occurs frequently in PM and rarely in DM.
- Skin findings in DM:
  - Heliotrope rash on the upper eyelids
  - Erythematous rash on the face
  - May also involve the back and shoulders (*shawl sign*), neck and chest (V shape), knees and elbows
  - Photosensitivity
  - *Gottron’s papules*: violaceous papules overlying dorsal interphalangeal or metacarpophalangeal areas, elbow, or knee joints
  - Nail cracking, thickening, and irregularity w/periungual telangiectasia
  - *Mechanic’s hand*: fissured, hyperpigmented, scaly, and hyperkeratotic; also associated w/↑ risk of ILD
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**Labs**
- ↑ CK (up to 50x above nl)
- ↑ Aldolase, AST, ALT, alk phos, LDH
- Anti–Jo-1 Abs: found in myositis w/associated ILD but are not specific for either DM or PM
- Others: electrolytes, TSH, Ca, and Mg to r/o other causes of weakness
- Bx: myopathic features (variation in fiber size, fiber splitting, fatty replacement of muscle tissue, and ↑ endomysial connective tissue) in addition to the following:
  - DM: perifascicular atrophy, membrane attack complex deposition along capillaries
  - PM: endomysial infiltrates composed of CD8+ T cells and macrophages invading non-necrotic muscle fibers that express MHC I antigen

**Imaging**
- CXR
- Video fluoroscopy or barium swallow study (r/o upper esophageal dysfunction)
- ECG (r/o cardiac involvement)
- EMG and NCS: consistent w/myopathic features

**Treatment**
- Prednisone
- IVIG or cyclophosphamide if pt fails to improve on prednisone or muscle enzymes begin rising when prednisone is tapered off
- Hydroxychloroquine for cutaneous lesions in DM
- Sun-blocking agents w/SPF ≥15 for skin protection in DM
- Physical therapy for gait training and ↑ muscle tone and strength
- Occupational therapy to assist w/ADLs
- Speech Rx for dysphagia and swallowing problems

### 23.3 INTERSTITIAL LUNG DISEASE (ILD)

**Definition**
ILD includes a large group of nonmalignant disorders characterized by diffuse damage to the lung parenchyma by inflammation and fibrosis or granulomatous reaction in interstitial or vascular areas.

**Diagnosis**

**H&P**
- Dyspnea
- Tachypnea
- Bibasilar end-inspiratory dry crackles
- Pulmonary HTN
- Cyanosis, clubbing
- ABGs: nl or may show respiratory alkalosis
- ANA, ANCA, ACE level, RF, LDH

**Imaging** *(Box 3-7)*
- CXR, HRCT: bibasilar reticular pattern

**PFTs**
- Well-defined patterns in PFTs are usually consistent w/restrictive defect (↓ FRC, RV, and TLC) due to ↓ lung compliance caused by alveolar wall thickening from inflammation and fibrosis. Diffusing capacity ↓ from inflammation and thickening of alveolar walls, although nonspecific. FEV1/FVC is usually nl or ↑ because lung stiffness keeps small airways open, although some conditions (e.g., sarcoidosis) may ↓ airflow.

**Treatment**
- Prednisone 0.5-1 mg/kg qd × 4-12 wk, then re-evaluate; if stable, taper; if not, maintain × another 4-12 wk; if still not improved, add cyclophosphamide or azathioprine
- Supplemental O2 PRN in pts w/hypoxemia; avoidance of tobacco and occupational exposures

**Clinical Pearls**
- Bronchoscopy and BAL may help identify type of ILD. However, role in defining stage of disease and response to Rx is controversial.
Box 3-7 • Radiographic Features That Suggest Specific Causes of Interstitial Lung Disease

<table>
<thead>
<tr>
<th>Hilar or Mediastinal Lymphadenopathy</th>
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<tbody>
<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Berylliosis</td>
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<tr>
<td>Silicosis (eggshell calcification)</td>
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<tr>
<td>Lymphocytic interstitial pneumonia</td>
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<tr>
<td>Amyloidosis</td>
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<td>Gaucher’s disease</td>
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<table>
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<tr>
<th>Pleural Disease</th>
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<tr>
<td>Asbestosis (pleural effusion, thickening, plaques, mesothelioma)</td>
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<tr>
<td>Systemic rheumatic disorders</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis (chylous effusion)</td>
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<tr>
<td>Nitrofurantoin</td>
</tr>
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<td>Radiation pneumonitis</td>
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<table>
<thead>
<tr>
<th>Pneumothorax</th>
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<tbody>
<tr>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
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<tr>
<td>Neurofibromatosis</td>
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<tr>
<td>Tuberous sclerosis</td>
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<table>
<thead>
<tr>
<th>Preserved Lung Volumes or Hyperinflation</th>
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<tbody>
<tr>
<td>Bronchiolitis obliterans organizing pneumonia</td>
</tr>
<tr>
<td>Chronic hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
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<tr>
<td>Sarcoidosis</td>
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<tr>
<td>Tuberous sclerosis</td>
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<th>Upper Lobe Distribution</th>
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<tbody>
<tr>
<td>Ankylosing spondylitis</td>
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<tr>
<td>Berylliosis</td>
</tr>
<tr>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Silicosis</td>
</tr>
<tr>
<td>Chronic hypersensitivity pneumonitis</td>
</tr>
<tr>
<td>Necrobiotic nodules of rheumatoid arthritis</td>
</tr>
</tbody>
</table>

• Bx is the most effective method for confirming dx and assessing disease activity.

**234 INTERSTITIAL NEPHRITIS**

**Definition**

Group of disorders affecting primarily the interstitium and renal tubules. Interstitial nephritis falls into 2 broad categories: acute and chronic.

- **Acute (AIN):** ↓ in renal function characterized histopathologically w/edema and inflammation of the renal interstitium, classically sparing the glomeruli and blood vessels. Most often induced by drugs.
- **Chronic (CIN):** characterized by interstitial fibrosis w/mononuclear leukocyte infiltration and tubular atrophy. It is a final common pathway of many chronic kidney diseases, including chronic bacterial infections, obstruction, and high-grade vesicoureteral reflux. Histopathologically seen as atrophy and fibrosis of the renal interstitium.

**Diagnosis**

*H&P*

- **AIN:**
  - Characteristically occurs during several days to weeks after an infection or initiation of a new medication
  - Classic triad—fever, rash, and arthralgias
  - Lumbar flank pain
  - Gross hematuria
  - Usually oliguric
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CIN:
- Sx related to the underlying cause (e.g., sarcoidosis, MM, urate nephropathy)
- Sx of renal failure (e.g., weakness, nausea, pruritus)
- HTN

Labs
- CBC: anemia, eosinophilia
- ↑ BUN, Cr
- U/A: eosinophiluria, hematuria, pyuria
- Proteinuria <3 g/24 hr
- Renal bx: indicated when dx is unclear and removal of offending agent does not result in improvement. Bx reveals infiltration of inflammatory cells into the interstitium w/interstitial edema and sparing of the glomeruli. In CIN, fibrotic scar tissue replaces the cellular infiltrate.

Imaging
- U/S of the kidneys: nl size kidneys in AIN and small contracted kidneys in CIN
- Gallium Ga 67 scan can be useful to discriminate between ATN and AIN.

Etiology
- AIN: drugs, infection, or associated w/imune or neoplastic disorders
  - Common drugs include PCN, methicillin, rifampin, cephs, TMP-SMZ, ciprofloxacin, NSAIDs, thiazides, furosemide, triamterene, allopurinol, phenytoin, captopril, and cimetidine
  - Infection (e.g., *Streptococcus, Legionella, Corynebacterium diphtheriae, Yersinia, Salmonella, HIV, EBV, CMV, Mycoplasma, Rickettsia*, and *Mycobacterium tuberculosis*)
  - Autoimmune causes of AIN: SLE, SS, Wegener’s granulomatosis
- CIN: PKD, urate nephropathy, analgesic nephropathy, sarcoidosis, MM, lead nephropathy, hypercalcemia, and Balkan nephropathy

Treatment
- ↓ Protein, potassium, and sodium diet; correction of underlying electrolyte abnormalities; IV hydration for hypercalcemia, BP control
- Corticosteroids 1 mg/kg/day × 4-6 wk in drug-induced AIN
- Cyclophosphamide 2 mg/kg/day × 4-6 wk added in pts not responding to corticosteroids
- Rx of CIN: directed at the underlying cause (e.g., corticosteroids for sarcoidosis, EDTA in lead nephropathy)

Clinical Pearl
- Once known mainly as a complication of strep infection, AIN today is most often due to drugs (88% of the time med started in previous 30 days).

IRRITABLE BOWEL SYNDROME (IBS)

Definition
Chronic functional disorder manifested by alteration in bowel habits and recurrent abd pain and bloating. IBS is a symptom complex influenced by a variety of physiologic determinants from gut to brain and back.

Diagnosis
The ROME III criteria:
- Recurrent abd pain or discomfort ≥3 days/mo in the past 3 mo associated w/≥2 of the following:
  - Pain relieved or improved w/defecation
  - Onset associated w/change in frequency of BM
  - Onset is associated w/change in the form or appearance of the stool
- Criteria must be fulfilled for ≥past 3 mo w/sx onset ≥6 mo before dx.

Treatment
- Lifestyle changes: exercise regularly; maintain adequate fiber and fluid intake; eliminate foods that aggravate sx; avoid caffeine, dairy products, fatty foods, and dietary excesses.
- Cognitive-behavioral therapy: may be useful because psychosocial stressors are important triggers of IBS.
Diseases

KAPOSI’S SARCOMA (KS)

Definition
Vascular neoplasm most frequently occurring in AIDS pts. It can be divided into the following four subsets:

- **Classic KS**: most frequently found in elderly Eastern European and Mediterranean men. It consists initially of violaceous macules and papules w/ subsequent development of plaques and red-purple nodules. Growth is slow, and most of the pts die of unrelated causes.
- **Epidemic or AIDS-related KS**: most frequently occurs in homosexual men. Lesions are generally multifocal and widespread. Lymphadenopathy may be associated.
- **Immunosuppression-associated or transplantation-associated KS**: usually associated w/ chemotherapy.

Diagnosis

**H&P**

- AIDS-related KS: multifocal and widespread red-purple or dark plaques or nodules on cutaneous or mucosal surfaces
- Generalized lymphadenopathy at the time of dx is present in >50% of pts w/ AIDS-related KS; the initial lesions have a rust-colored appearance; subsequent progression to red or purple nodules or plaques occurs.
- Most frequently affected areas are the face, trunk, oral cavity, UEs, and LEs.

**Labs**

- HIV, CBC

Etiology

- Herpesvirus (HHV-8, KS-associated herpesvirus, KSHV). It can be transmitted sexually (homosexual, heterosexual activities) and by other forms of nonsexual contact, such as maternal-infant transmission (common in African countries).

Treatment

- Excisional bx often provides adequate treatment of single lesions and resected recurrences in classic KS.
- Liquid nitrogen cryotherapy can result in complete response in 80% of lesions.
- Interlesional chemotherapy w/vinblastine; RT useful for nodular lesions >1 cm in diameter. Intralesional injection of interferon alfa-2b is also effective.
- RT is effective in non-AIDS KS and for large tumor masses that interfere w/nl function.
- Interferon: effective in AIDS-related KS and is often used in combination w/AZT.
- Systemic chemo (vinblastine [or etoposide], bleomycin, doxorubicin, and dacarbazine): used for rapidly progressive disease and for classic and African endemic KS.
- Sirolimus: effective in inhibiting the progression of dermal KS in kidney transplant recipients.
- Paclitaxel: effective in advanced KS and represents an excellent second-line Rx.

Clinical Pearl

- Immunosuppression-associated KS usually regresses w/ cessation, reduction, or modification of immunosuppression Rx in most pts. Similarly, in HIV pts, KS responds concurrently w/ ↓ in serum HIV RNA and ↑ in CD4 count.
237 KORSAKOFF’S PSYCHOSIS

Definition
Disorder of learning and memory associated with thiamine deficiency. It is classically seen in alcoholics and may follow the presentation of Wernicke’s encephalopathy.

Diagnosis
H&P
- Impairment of ability to remember new material
- Remote memory is said to be retained but is almost universally diminished on careful testing.
- Confabulation may occur.

Labs
- ↑ Serum pyruvate
- ↓ Whole blood or erythrocyte transketolase; rapid resolution to nl in 24 hr with thiamine repletion

Imaging
- MRI: diencephalic and mesencephalic lesions may be present.

Etiology
- Thiamine deficiency, commonly in alcoholics or other malnourished populations, although it may be iatrogenic from prolonged infusion of dextrose-containing fluids w/o thiamine repletion.

Treatment
- Thiamine 100 mg IV or IM. Typical duration of IV treatment is 3-5 days.
  - Avoid dextrose-containing fluids until thiamine is repleted.
- Thiamine given acutely during Wernicke’s phase (disorders of extraocular movements, confusion, and ataxia) may prevent the development of Korsakoff’s psychosis.

238 LABYRINTHITIS

Definition
Peripheral vestibulopathy associated with hearing loss. The term vestibular neuronitis is used when hearing is not affected.

Diagnosis
H&P
- Vertigo, N/V
- During the first day, the pt usually has difficulty focusing the eyes because of spontaneous nystagmus.
- Sx usually peak within 24 hr, then resolve gradually during several weeks.

Imaging
- Usually not necessary
- MRI of the brain w/ and w/o contrast w/fine cuts through the internal auditory canal if cranial nerve exam is abnl or eighth nerve tumor is suspected

Treatment
- Antiemetics
- Vestibular suppressant: meclizine 12.5-25 mg qid often used; scopolamine patch also effective
- Prednisone taper for resistant cases

239 LACTOSE INTOLERANCE

Definition
Insufficient concentration of lactase enzyme, leading to fermentation of malabsorbed lactose by intestinal bacteria w/subsequent production of intestinal gas and various organic acids.

Diagnosis
H&P
- Clinical presentation: abd tenderness and cramping, bloating, flatulence, diarrhea about 2 hr after ingestion of lactose
- PE: usually nl
**Chapter 3  Diseases and Disorders**

**Labs**
- Lactose breath hydrogen test: breath hydrogen >20 ppm within 90 min of ingestion of 50 g of lactose
- The lactose tolerance test: older and less accurate testing modality (20% rate of false-positive and false-negative results)

**Etiology**
- Secondary lactose intolerance: usually a result of injury of the intestinal mucosa (Crohn’s disease, viral gastroenteritis, AIDS enteropathy, cryptosporidiosis, Whipple’s disease, sprue)
- Congenital lactase deficiency: common in premature infants; rare in full-term infants and generally inherited as a chromosomal recessive trait

**Treatment**
- Lactose-free diet
- Addition of lactase enzyme supplement (Lactaid tablets, Dairy Ease) before the ingestion of milk products may prevent sx in some pts.
- Ensure adequate Ca intake. Ca supplementation is recommended to prevent osteoporosis.

**LAMBERT-EATON MYASTHENIC SYNDROME**

**Definition**
Disorder of neuromuscular transmission caused by Ab against presynaptic voltage-gated P/Q Ca channels on motor and autonomic nerve terminals. There are 2 forms: paraneoplastic (most common) and non-paraneoplastic (autoimmune).

**Diagnosis**
**H&P**
- Weakness w/↓ or absent muscle stretch reflexes
- Proximal LE muscles affected most
- Transient strength improvement w/brief exercise
- Autonomic dysfunction common (dry mouth in 75%, sexual dysfunction, blurred vision, constipation, orthostasis)

**EMG/NCS**
- ↓ Motor amplitudes w/nil sensory studies; >10% decrement in motor amplitudes on slow repetitive nerve stimulation (RNS) at 2-3Hz, w/>100% increment on fast RNS (20-30 HZ) or immediately after 10 sec of max exercise (post-exercise facilitation)

**Treatment**
- Plasma exchange (200-250 mL/kg over 10-14 days) or IV immune globulins (2 g/kg over 2-5 days)
- Chronic Rx
  - Anticholinesterase agents (pyridostigmine 30-60 mg q4-6h)
  - Guanidine hydrochloride: 5-10 mg/kg/day initially
  - Prednisone 1.0-1.5 mg/kg/day tapered over months to min. effective dose
  - Azathioprine given alone or in combination w/prednisone; can substitute w/cyclosporine in intolerant pts
  - Fludrocortisone or midodrine for orthostatic hypotension
  - Rx of underlying malignant disease if present

**Clinical Pearl**
- Presentation w/Lambert-Eaton myasthenic syndrome may precede dx of SCLC by up to 5 yr.

**LEAD POISONING**

**Diagnosis**
**H&P**
- Myalgias, irritability, headache, and general fatigue present initially
- Abd cramping, constipation, weight loss, tremor, paresthesias and peripheral neuritis, seizures, and coma w/severe toxicity
- Motor neuropathy is common in children w/lead poisoning; learning disorders are also frequent.
Labs
- Venous blood lead level: nl level = <10 µg/dL; levels of 50-70 µg/dL indicative of moderate toxicity; levels >70 µg/dL associated w/severe poisoning
- Mild anemia w/basophilic stippling on peripheral smear
- ↑ Zinc protoporphyrin levels or free erythrocyte protoporphyrin level
- An ↑ body burden of lead w/previous high-level exposure in pts w/occupational lead poisoning can be demonstrated by measuring the excretion of lead in urine after premedication w/CaEDTA or another chelating agent.

Etiology
- Chronic repeated exposure to paint containing lead, plumbing, storage of batteries, pottery, lead soldering. Concentration of lead is generally highest in lead-based paint on exterior surfaces. Among interior surfaces, windows are most likely to have highest lead content.

Treatment
- Chelation Rx in children w/blood lead levels ≥45 µg/dL:
  - Succimer (DMSA) 10 mg/kg PO q8h for 5 days, then q12h for 2 wk, can be used in pts w/levels between 45 and 70 µg/dL.
  - Edetate Ca disodium (EDTA) and dimercaprol (BAL) are effective in pts w/severe toxicity.
  - Use of both EDTA and DMSA is indicated in children w/blood levels >70 µg/dL.
  - d-Penicillamine (Cuprimine) can also be used for lead poisoning, but it is not FDA approved for this condition.
- Children w/blood levels 20-44 µg/dL: case management by a qualified social worker, clinical management, environmental assessment, and lead hazard control. Chelation Rx should be considered in children w/refractory blood lead levels.
- Children w/blood levels 10-19 µg/dL: adequate amounts of Ca, iron, zinc, and protein in pt’s diet; pt and parental education

Clinical Pearls
- Lead poisoning is most common in children aged 1-5 yr (17,000 cases/100,000 persons). The highest rates are among blacks, those w/low income, and urban children.
- Pts w/mild to moderate toxicity generally improve w/o any residual deficits. The presence of encephalopathy at dx is a poor prognostic sign. Residual neurologic deficits may persist in these pts.

242 LEUKEMIA, ACUTE LYMPHOCYTIC (ALL)

Definition
Disorder characterized by uncontrolled proliferation of abnl, immature lymphocytes and their progenitors, ultimately replacing nl bone marrow elements.

Diagnosis
H&P
- Skin pallor, purpura, or easy bruising
- Lymphadenopathy or hepatosplenomegaly
- Fever, bone pain, oliguria, weakness, weight loss, ΔMS

Labs
- CBC: normochromic, normocytic anemia; thrombocytopenia
- Peripheral smear: lymphoblasts
- Special diagnostic tests include immunophenotyping, cytogenetics, and cytochemistry.
- The French-American-British (FAB) Cooperative Study Group has classified ALL into 3 groups (L1 to L3) based on cell size, cytoplasmic appearance, nucleus shape, and chromatin pattern (Table 3-27); the most common form is the L2 type.
- Immunologic classification is on the basis of expression of surface antigens by blast cells: T lineage and B lineage.
Diseases

imaging

- CXR to evaluate for the presence of mediastinal mass
- CT scan or U/S of abd/pelvis to assess splenomegaly or leukemic infiltration of abd organs

epilogue

- Risk in pts w/a previous use of antineoplastic agents (e.g., chemotherapy of NHL, Hodgkin’s disease, ovarian cancer, myeloma)
- Environmental factors (e.g., ionizing radiation), toxins (e.g., benzene)

treatment

- Emergency treatment in pts w/intracerebral leukostasis. It consists of one or more of the following:
  - Cranial irradiation of the whole brain in one- or two-dose fractions
  - Leukapheresis
  - Oral hydroxyurea (requires 48-72 hr to significantly ↓ the circulating blast count)
- Prevent urate nephropathy by vigorous hydration, allopurinol, and urine alkalinization w/acetazolamide.
- Rx infections w/broad-spectrum abx.
- Correct significant thrombocytopenia (platelet counts <20,000/mm³) w/platelet transfusion.
- Induction Rx is intensive chemotherapy to destroy a significant number of leukemic cells and to achieve remission.
- Consolidation Rx consists of an aggressive course of chemotherapy w/ or w/o radiotherapy shortly after complete remission has been obtained. Its purpose is to prolong the remission period or cure.
- Meningeal prophylactic Rx w/intrathecal MTX w/ or w/o cranial irradiation to prevent meningeal sequestration of leukemic cells
- The goal of maintenance Rx is to maintain a state of remission. In pts w/ALL, intermittent Rx is continued for at least 3 yr.
- Bone marrow transplant: pts should receive allograft in the first complete remission if they are between 20-50 yr and have matched a sibling donor.

clean pearls

- Prognosis is generally poorer in adult disease compared w/childhood disease (40% adult cure rate vs. 80% cure rate in children).
- Five-year leukemia-free survival is <40%.

243 LEUKEMIA, ACUTE MYELOGENOUS (AML)

Definition
Disorder characterized by uncontrolled proliferation of primitive myeloid cells (blasts), ultimately replacing nl bone marrow elements, frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia) w/ or w/o leukocytosis.

Diagnosis
H&P
Pts generally come to medical attention because of the effects of the cytopenias:
- Anemia is manifested w/weakness or fatigue.
- Thrombocytopenia can be manifested w/bleeding, petechiae, and ecchymosis.
- Neutropenia can result in infections and fever.
- PE may reveal skin pallor, bruises, petechiae; abd exam may reveal hepatosplenomegaly; peripheral lymphadenopathy may also be present.
- Hyperleukocytosis can lead to sx of leukostasis, such as ocular and cerebrovascular dysfunction or bleeding.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 ALL, childhood variant</td>
<td>Small, uniform blasts, nucleoli indistinct</td>
</tr>
<tr>
<td>L2 ALL, adult variant</td>
<td>Larger, more irregular nucleoli present</td>
</tr>
<tr>
<td>L3, Burkitt-like ALL</td>
<td>Large w/strongly basophilic cytoplasm and vacuoles</td>
</tr>
</tbody>
</table>

TABLE 3-27 Classification of ALL
Chapter 3  Diseases and Disorders

**LEUKEMIA, ACUTE MYELOGENOUS**

**LEUKEMIA, ACUTE MYELOGENOUS**

**TABLE 3-28 Classification of AML**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Morphology</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0, acute undifferentiated leukemia</td>
<td>Uniform, very undifferentiated</td>
</tr>
<tr>
<td>M1, acute myeloid leukemia w/minimal differentiation</td>
<td>Very undifferentiated, few azurophilic granules</td>
</tr>
<tr>
<td>M2, acute myeloid leukemia w/differentiation</td>
<td>Granulated blasts predominate; Auer rods may be seen</td>
</tr>
<tr>
<td>M3, acute promyelocytic leukemia</td>
<td>Hypergranular promyelocytes</td>
</tr>
<tr>
<td>M4, acute myelomonocytic leukemia</td>
<td>Both monoblasts and myeloblasts are present</td>
</tr>
<tr>
<td>M4E</td>
<td>Like M4 but w/eosinophils</td>
</tr>
<tr>
<td>M5, acute monocytic leukemia</td>
<td>Monoblasts predominate</td>
</tr>
<tr>
<td>M5a</td>
<td>80% monoblasts</td>
</tr>
<tr>
<td>M5b</td>
<td>&lt;20% promonocytes</td>
</tr>
<tr>
<td>M6, acute erythroleukemia</td>
<td>Erythroblasts and megaloblastic RBC precursors seen</td>
</tr>
<tr>
<td>M7, acute megakaryocytic leukemia</td>
<td>Undifferentiated blasts</td>
</tr>
</tbody>
</table>

**Imaging**
- **CXR** is useful to evaluate for the presence of mediastinal masses.
- **CT scan of the abd** may reveal hepatosplenomegaly or leukemic involvement of other organs.

**Etiology**
- Risk factors are previous use of antineoplastic agents, chromosomal abnormalities, ionizing radiation, toxins, immunodeficiency states, and chronic myeloproliferative disorders.

**Treatment**
- **Intracerebral leukostasis:**
  - Cranial irradiation
  - Leukapheresis
  - Oral hydroxyurea
- **Urate nephropathy prevention w/vigorous hydration, allopurinol, and urine alkalization w/acetazolamide**
- **Broad-spectrum abx for infections**
- **Platelet transfusions for significant thrombocytopenia**
- **Intensive induction chemotherapy to destroy leukemic cells and to achieve remission**
- The duration of remission is variable; the median duration of remission in an adult w/AML is 1 yr.
Consolidation Rx consists of an aggressive course of chemotherapy w/ or w/o radiation therapy shortly after complete remission has been obtained; its purpose is to prolong the remission period or cure. Complications of consolidation Rx are usually secondary to severe bone marrow suppression (anemia, thrombocytopenia, granulocytopenia).

Autologous bone marrow transplantation: indicated in pts <55 yr w/o a sibling donor. Allogeneic bone marrow transplantation is generally available to <20% of pts; usually performed only in pts <40 yr of age because of higher incidence of GVHD w/advancing age.

Clinical Pearls
- Remission can be achieved in nearly 80% of pts <55 yr of age. Remission rates are highest in children.
- Cure with allogeneic bone marrow transplantation: 60%.

# LEUKEMIA, CHRONIC LYMPHOCYTIC (CLL)

## Definition
Lymphoproliferative disorder characterized by proliferation and accumulation of mature-appearing neoplastic lymphocytes.

### Diagnosis
H&P
- Variable clinical presentation according to stage of the disease. Some pts come to medical attention because of weakness and fatigue (secondary to anemia) or lymphadenopathy. Many cases are diagnosed on the basis of lab results obtained after routine PE.

### Labs
- Proliferative lymphocytosis (≥15,000/dL) of well-differentiated lymphocytes is the hallmark of CLL.
- There is monotonous replacement of the bone marrow by small lymphocytes (marrow contains ≥30% of well-differentiated lymphocytes).
- Hypogammaglobulinemia and ↑ LDH may be present at the time of dx.
- Anemia or thrombocytopenia, if present, indicate poorer prognosis.

### Staging (Table 3-29)
- The pt’s prognosis is directly related to the clinical stage (e.g., the average survival in pts in Rai stage 0 or Binet stage A is >120 mo; whereas for Rai stage 4 or Binet stage C, it is approximately 30 mo). Overall 5-yr survival is 60%.

## TABLE 3-29: Rai and Binet Staging Systems in Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Rai stage</th>
<th>Lymphocytosis</th>
<th>Lymphadenopathy</th>
<th>Hepatomegaly or Splenomegaly</th>
<th>Hemoglobin (g/dL)</th>
<th>Platelets × 10^9/µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>≥11</td>
<td>≥100</td>
</tr>
<tr>
<td>I</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>≥11</td>
<td>≥100</td>
</tr>
<tr>
<td>II</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>≥11</td>
<td>≥100</td>
</tr>
<tr>
<td>III</td>
<td>±</td>
<td>±</td>
<td>−</td>
<td>&lt;11</td>
<td>≥100</td>
</tr>
<tr>
<td>IV</td>
<td>±</td>
<td>±</td>
<td>±</td>
<td>Any</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Binet stage</th>
<th>Lymphocytosis</th>
<th>Lymphadenopathy</th>
<th>Hepatomegaly or Splenomegaly</th>
<th>Hemoglobin (g/dL)</th>
<th>Platelets × 10^9/µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+</td>
<td>±</td>
<td>± (&lt;3 lymphatic groups* positive)</td>
<td>≥10</td>
<td>≥100</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>±</td>
<td>± (≥3 lymphatic groups* positive)</td>
<td>≥10</td>
<td>≥100</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>±</td>
<td>±</td>
<td>&lt;10 and/or &lt;100</td>
<td></td>
</tr>
</tbody>
</table>

*(1) Cervical, axillary, and inguinal nodes; (2) liver; and (3) spleen; each group is considered one group whether it is unilateral or bilateral.
### Chapter 3  
Diseases and Disorders

#### Treatment
- Rai stage 0 or Binet stage A: observation
- Symptomatic pts in Rai stages I and II or Binet stage B: chlorambucil or fludarabine; local irradiation for isolated symptomatic lymphadenopathy and lymph nodes that interfere w/vital organs
- Rai stages III and IV, Binet stage C: chlorambucil chemotherapy w/ or w/o prednisone
  - Fludarabine, CAP (cyclophosphamide, doxorubicin [Adriamycin], prednisone), or cyclophosphamide, doxorubicin, vincristine, and prednisone (mini-CHOP) can be used in pts who respond poorly to chlorambucil.
  - Splenic irradiation can be used in selected pts w/advanced disease.
- Erythropoietin: for anemia that is unresponsive to other measures

#### Clinical Pearl
- Trisomy 12 is the most common chromosomal abnormality, followed by 14q+, 13q, and 11q; these all indicate a poor prognosis.

### Box 3-8  
Classification of Chronic Myelogenous Leukemia

#### Chronic Phase
- Asymptomatic after Rx
- No features of accelerated phase or blast crisis

#### Accelerated Phase
- Leukocyte count increasingly difficult to control w/standard Rx
- ↑ Blast percentage
  - >10% in blood or bone marrow
  - >20% blasts plus promyelocytes in blood or bone marrow
  - >20% basophils plus eosinophils in blood
- Progressive anemia or thrombocytopenia
- New cytogenetic abnormalities, especially a second Ph chromosome or trisomy 8
- Worsening constitutional sx
- Progressive splenomegaly
- Development of myeloblastomas or myelofibrosis

#### Blast Crisis
- >30% blasts plus promyelocytes in blood or bone marrow

#### Diagnosis

**H&P**
- 40% of pts are asymptomatic and dx is based solely on an abnl blood count. Common complaints at the time of dx are weakness and discomfort secondary to an enlarged spleen (abd discomfort or pain). Splenomegaly is present in up to 40% of pts at time of dx.

** Labs**
- ↑ WBC count (generally >100,000/mm³) w/broad spectrum of granulocytic forms
- Bone marrow: hypercellularity w/granulocytic hyperplasia, ↑ ratio of myeloid cells to erythroid cells, and ↑ number of megakaryocytes. Blasts and promyelocytes constitute <10% of all cells.
- Leukocyte alkaline phosphate markedly ↓ (used to distinguish CML from other myeloproliferative disorders)
- Anemia and thrombocytosis are often present.
Etiology
- Philadelphia chromosome [chromosome translocation t(9;22)(q34;q11.2)] present in >95% of pts

Treatment
- Imatinib mesylate (Gleevec): >60% of pts have major cytogenetic response (<35% Ph+ cells in the marrow), and >80% have progression-free survival after 24 mo. Nilotinib can be used for Rx of Ph+ chronic- or accelerated-phase CML in pts resistant to or intolerant of imatinib.
- Symptomatic hyperleukocytosis (e.g., CNS sx): leukapheresis and hydroxyurea
- Allogeneic stem cell transplantation is the only curative treatment of CML in chronic phase unresponsive to imatinib or nilotinib. It should be considered in “young” pts (↑ survival in pts <55 yr) w/compatible siblings.

Clinical Pearl
- Philadelphia chromosome presence (Ph1) survival rate is 8 × > that of those w/o it.

246 LEUKEMIA, HAIRY CELL

Definition
Lymphoid neoplasm characterized by the proliferation of mature B cells w/prominent cytoplasmic projections (hairs).

Diagnosis

H&P
- PE: splenomegaly (>90% of cases) secondary to tumor cell infiltration

Labs
- CBC: pancytopenia involving erythrocytes, neutrophils, and platelets
- Peripheral smear: hairy cells (5%-80% of cells in the peripheral blood). The cytoplasmic projections on the cells are redundant plasma membranes.
- Leukemic cells stain + for tartrate-resistant acid phosphatase (TRAP).
- Bone marrow may result in a “dry tap” (because of ↑ marrow reticulin).

Treatment
- 2-Chloro-2’-deoxyadenosine (CdA, cladribine) or 2’-deoxycoformycin (dCF, pentostatin)

247 LISTERIOSIS

Definition
Systemic infection caused by the gram-positive aerobic bacterium Listeria monocytogenes.

Diagnosis

H&P
- Infections in pregnancy
  - More common in third trimester
  - Fever and chills w/o localizing sx or signs of infection
- Meningoencephalitis
  - More common in neonates and immunocompromised pts
  - Neonates: poor appetite w/ or w/o fever
  - Adults: presentation often subacute, w/low-grade fever and personality change as only signs
  - Focal neurologic signs seen w/o demonstrable brain abscess on CT scan
- Cerebritis/rhomencephalitis
  - Headache and fever
  - Progressive cranial nerve palsies, hemiparesis, seizures, depressed level of consciousness, cerebellar signs, respiratory insufficiency
- Focal infections
  - Ocular infections (purulent conjunctivitis) and skin lesions (granulomatosis infantisepticum) as a result of inadvertent inoculation by lab and veterinary personnel
  - Others: arthritis, prosthetic joint infections, peritonitis, osteomyelitis, organ abscesses, cholecystitis
LIVER FAILURE

Diagnosis

**Pertinent Hx**
- Hepatitis, HIV, CMV
- Ethanol intake
- Drug hx and exposure to toxins
- IV drug abuse
- H/o cirrhosis
- Heat exposure (heat stroke)
- Measles, influenza w/ASA use (Reye’s syndrome)
- H/o carcinoma (primary or metastatic)
- Autoimmune disorders (autoimmune hepatitis)
- Acetaminophen intake, particularly in starved alcoholic pt (acetaminophen toxicity is exaggerated by starvation and any drug that induces the cytochrome P-450 isoenzyme [e.g., ethanol])

**PE**
- Stigmata of cirrhosis in pts w/progression of cirrhosis to hepatic failure
- Jaundice
- Asterixis
- Fetal hepaticus
- Evidence of sepsis (fever, leukocytosis) or shock
- Agitation and delirium are common and often abrupt in pts w/acute liver failure, occasionally preceding the appearance of jaundice.
- Hypotension, hypovolemia, oliguria

**Labs (Table 3-30)**
- LFTs
  - Alcoholic hepatitis: mild ↑ of AST and ALT (usually <500 U/L; AST > ALT [2:1])
  - ↑ Bili (except in Reye’s syndrome); >20 mg/dL indicates poor prognosis
  - Alk phos only modestly ↑ (markedly ↑ in extrahepatic obstruction, PBC, and carcinoma of liver)
- Anemia, leukocytosis
- Hypoglycemia (caused by defective gluconeogenesis and ↑ peripheral insulin levels as a result of inadequate hepatic uptake)
- ↑ BUN, Cr (prerenal azotemia, HRS); BUN level may be nl in end-stage liver disease.
- Hypokalemia, hyponatremia, hypophosphatemia
- ↑ INR, ↑ APTT, ↓ platelets (if splenomegaly is present)
<table>
<thead>
<tr>
<th>Test</th>
<th>Toxic or Ischemic</th>
<th>Viral</th>
<th>Alcohol</th>
<th>Chronic Complete</th>
<th>Chronic Partial</th>
<th>Acute Complete (first 24 hr)</th>
<th>Infiltration (Chronic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminotransferases</td>
<td>50-100×</td>
<td>5-50×</td>
<td>2-5×</td>
<td>1-5×</td>
<td>1-5×</td>
<td>1-50×</td>
<td>1-3×</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>1-3×</td>
<td>1-3×</td>
<td>1-10×</td>
<td>2-20×</td>
<td>2-10×</td>
<td>May be nl</td>
<td>1-20×</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1-5×</td>
<td>1-30×</td>
<td>1-30×</td>
<td>1-30×</td>
<td>1-5×</td>
<td>Usually nl</td>
<td>1-5×</td>
</tr>
<tr>
<td>PT</td>
<td>Prolonged in severe cases, unresponsive to vitamin K</td>
<td></td>
<td></td>
<td>May be prolonged, responsive to vitamin K</td>
<td>Usually nl</td>
<td>Usually nl</td>
<td>Usually nl</td>
</tr>
<tr>
<td>Albumin</td>
<td>NI in acute illness, may be ↓ in chronic illness</td>
<td></td>
<td></td>
<td>Usually nl, but may be ↓ in biliary cirrhosis</td>
<td>Usually nl</td>
<td>Usually nl</td>
<td>Usually nl</td>
</tr>
<tr>
<td>Typical disorders</td>
<td>Acetaminophen toxicity, shock liver</td>
<td>Acute hepatitis A or B</td>
<td>Alcoholic hepatitis</td>
<td>Pancreatic carcinoma</td>
<td>Sclerosing cholangitis</td>
<td>Choledocholithiasis</td>
<td>Primary or metastatic carcinoma, Mycobacterium avium-intracellulare infection</td>
</tr>
</tbody>
</table>
LONG QT SYNDROME (LQTS)

Definition
ECG abnormality characterized by a corrected QT interval >0.44 sec and associated with risk for development of life-threatening ventricular arrhythmias.

Diagnosis
H&P
- Palpitations, presyncope
- Syncope caused by VT
- Sudden death
- Familial (associated with deafness): autosomal recessive
- Familial associated with normal hearing: autosomal dominant (the incidence is unknown). Although inheritance of LQTS is autosomal dominant, female predominance has often been observed and has been attributed to an increased susceptibility to cardiac arrhythmias in women.

ECG
- Diagnostic criteria for the congenital LQTS are given in Table 3-31.

Etiology
- Cardiac repolarization abnormality
- Congenital cause (chromosome 3 or chromosome 7 abnormality)
- Acquired causes:
  - Drugs (dofetilide, ibutilide, bepridil, quinidine, procainamide, sotalol, amiodarone, ranolazine, disopyramide, phenothiazines and antiemetic agents [droperidol, domperidone], tricyclic antidepressants, quinolones, methadone, astemizole or cisapride given with ketoconazole or...
erythromycin, clarithromycin, and antimalarials), particularly among pts w/asthma or those using potassium-lowering medications.

- Hypokalemia, hypomagnesemia, hypocalcemia
- Liquid protein diet
- CNS lesions
- MVP
- Hypothyroidism

Treatment

- Asymptomatic sporadic forms w/no complex ventricular arrhythmias: no treatment
- Risk stratification.
  - High risk (>50% of cardiac event): QTc >500 ms and LQT1 and LQT2 or male pt w/LQT3
  - Moderate risk (30%-50%): QTc >500 ms in female pt w/LQT3 or QTc <500 ms in male pt w/LQT3 or in female pt w/LQT2 or 3
  - Low risk (<30%): QTc <500 ms and LQT1 or male pt w/LQT2
- General recommendations:
  - Avoid competitive sports.
  - β-Blocker at max tolerated dose
  - Cardiology referral is recommended for all cases.
  - Pacemaker and implantable defibrillator are recommended for survivors of cardiac arrest, for pts w/syncope while receiving β-blockers, and for primary prevention in pts w/characteristics that suggest ↑risk (these include LQT2, LQT3, and QTc interval >500 ms).

Clinical Pearls

- The timing and frequency of syncope, QTc prolongation, and sex are predictive of risk for aborted cardiac arrest and sudden cardiac death during adolescence. Higher risk is present in those w/syncope in the last 10 yr compared with those w/no syncopal episodes, those w/QTc ≥530 ms, and males between ages of 10 and 12 yr.
- The FHx should assess not only a h/o sudden death but also other deaths that may have occurred as manifestations of LQTS (e.g., sudden infant death, drowning, loss of consciousness while driving).

**TABLE 3-31 ECG Criteria for Congenital Long QT Syndrome**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corrected QT &gt;480 ms</td>
<td>3</td>
</tr>
<tr>
<td>Corrected QT 460-480 ms</td>
<td>2</td>
</tr>
<tr>
<td>Corrected QT 450-460 ms (men)</td>
<td>1</td>
</tr>
<tr>
<td>Torsades de pointes</td>
<td>2</td>
</tr>
<tr>
<td>T-wave alternans</td>
<td>1</td>
</tr>
<tr>
<td>Notched T wave in 3 leads</td>
<td>1</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>0.5</td>
</tr>
<tr>
<td>Syncope w/stress</td>
<td>2</td>
</tr>
<tr>
<td>Syncope w/o stress</td>
<td>1</td>
</tr>
<tr>
<td>Congenital deafness</td>
<td>0.5</td>
</tr>
<tr>
<td>Definite FHx of long QT</td>
<td>1</td>
</tr>
<tr>
<td>Unexplained cardiac death in first-degree age &lt;30 yr</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Total score = 4: definite long QT syndrome.
Total score 2 to 3: intermediate probability.
Total score = 1: low probability.

**250 LUNG NEOPLASM**

**Definition**

Malignant neoplasm arising from lung tissue. The WHO distinguishes 12 types of pulmonary neoplasms. Among them, the major types are **squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma** (Table 3-32). However, the crucial difference in the dx of lung cancer is between...
small cell (SCLC) and non–small cell (NSCLC) types because the prognosis and therapeutic approach are different.

**Diagnosis**

**H&P**
- Cough, hemoptysis, dyspnea, wheezing
- Chest, shoulder, and bone pain
- Weight loss, fatigue, fever, anorexia, dysphagia
- Paraneoplastic syndromes:
  - *Lambert-Eaton syndrome*: myopathy involving proximal muscle groups
  - Endocrine manifestations: hypercalcemia, ectopic ACTH, SIADH
  - Neurologic: subacute cerebellar degeneration, peripheral neuropathy, cortical degeneration
  - Musculoskeletal: polymyositis, clubbing, hypertrophic pulmonary osteoarthropathy
  - Hematologic or vascular: migratory thrombophlebitis, marantic thrombosis, anemia, thrombocytosis, or thrombocytopenia
  - Cutaneous: acanthosis nigricans, dermatomyositis
- Pleural effusion (10% of pts), recurrent pneumonias (secondary to obstruction), localized wheezing
- SVC syndrome
- Horner’s syndrome: constricted pupil, ptosis, facial anhidrosis caused by spinal cord damage between C8 and T1 secondary to a superior sulcus tumor (bronchogenic carcinoma of the extreme lung apex); a superior sulcus tumor associated w/ipsilateral Horner’s syndrome and shoulder pain is known as a *Pancoast tumor*.

**Labs**
- Flexible fiberoptic bronchoscopy: brush and bx specimens are obtained from any visualized endobronchial lesions.
- Transthoracic FNAB w/fluoroscopic or CT scan guidance to evaluate peripheral pulmonary nodules
- Mediastinoscopy and anteromedial sternotomy in suspected tumor involvement of the mediastinum
- Labs: CBC, Ca, alb, ALT, Cr, LDH, ABGs, metabolic panel
- Consider bone marrow in selected pts w/SCLC w/↑ LDH or cytopenia.
- PFTs: to determine if the pt can tolerate any loss of lung tissue. Pneumonectomy is possible if the pt has a preoperative FEV₁ ≥2 L or if the maximal voluntary ventilation is >50% of predicted capacity. Individuals w/FEV₁ >1.5 L are suitable for lobectomy w/o further evaluation unless there is evidence of ILD or undue dyspnea on exertion. In that case, DLCO should be measured. If the DLCO is <80% predicted nl, the pt is not clearly operable.
**Imaging**
- CXR
- CT chest
- PET w/^{18}F-fluorodeoxyglucose (^{18}FDG-PET): for preop staging of NSCLC
- CT of liver and brain; bone scan in all pts w/SCLC and pts w/NSCLC suspected of involving these organs

**Staging**
After confirmation of dx, pts should undergo staging:
- The international staging system for NSCLC: Stage I (N0 [no lymph node involvement]). Stage II (N1 [spread to ipsilateral bronchopulmonary or hilar lymph nodes]) includes localized tumors for which surgical resection is the preferred treatment. Stage III is subdivided into IIIA (potentially resectable) and IIIB. The surgical management of stage IIIA disease (N2 [involvement of ipsilateral mediastinal nodes]) is controversial. Only 20% of N2 disease is considered min. disease (involvement of only one node) and technically resectable. Stage IV indicates metastatic disease. The pathologic staging system uses a tumor–nodal involvement–metastasis system.
- In pts w/SCLC, the staging system from the Veterans Administration Lung Cancer Study Group contains 2 stages:
  - Limited stage disease: confined to the regional lymph nodes and to one hemithorax (excluding pleural surfaces)
  - Extensive stage disease: spread beyond the confines of limited stage disease

**Etiology**
- Tobacco abuse
- Environmental agents (e.g., radon) and industrial agents (e.g., ionizing radiation, asbestos, nickel, uranium, vinyl chloride, chromium, arsenic, coal dust)

**Treatment**

**NSCLC**
- Surgical resection
  - Indicated in pts w/limited disease (not involving mediastinal nodes, ribs, pleura, or distant sites). This represents 15%-30% of diagnosed cases.
  - Preoperative chemotherapy: consider in pts w/more advanced disease (stage IIIA) who are being considered for surgery. Gene expression profiles that predict the risk of recurrence in pts w/early-stage (IA) NSCLC have been identified. These pts are at high risk for recurrence and may also benefit from adjuvant chemotherapy.
  - Postoperative adjuvant chemotherapy (chemotherapy given after surgical resection of an apparently localized tumor to eradicate occult mets) w/vinorelbine plus cisplatin: consider in pts w/completely resected stage IB or stage II NSCLC and good performance status. Adjuvant chemotherapy is generally indicated for pts w/resected stages IIA through IIIA.
- Treatment of unresectable NSCLC:
  - Radiotherapy can be used alone or in combination w/chemotherapy; it is used primarily for treatment of CNS and skeletal mets, SVC, and obstructive atelectasis; although thoracic radiotherapy is generally considered standard Rx for stage III disease, it has limited effect on survival. Palliative radiotherapy should be delayed until sx occur because immediate Rx offers no advantage over delayed Rx and results in more adverse events from the radiotherapy.
  - Chemotherapy: current drugs of choice are paclitaxel + either carboplatin or cisplatin; cisplatin + vinorelbine; gemcitabine + cisplatin; carboplatin or cisplatin + docetaxel. The overall results are disappointing, and none of the standard regimens for NSCLC is clearly superior to the others. The addition of bevacizumab to paclitaxel + carboplatin results in significant survival benefit but carries an ↑ risk of treatment-related death. Gefitinib and erlotinib are oral inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase. Both agents are approved only for pts who have failed at least one prior chemotherapy regimen.
• The addition of chemotherapy to radiotherapy improves survival in pts w/locally advanced, unresectable NSCLC. The absolute benefit is relatively small, however, and should be balanced against the ↑ toxicity associated w/the addition of chemotherapy.

**SCLC**
- Limited stage disease: standard treatments include thoracic radiotherapy and chemotherapy (cisplatin and etoposide).
- Extensive stage disease: standard treatments include combination chemotherapy (cisplatin or carboplatin + etoposide or combination of irinotecan and cisplatin).
- Prophylactic cranial irradiation: for pts in complete remission to ↓ the risk of CNS metastasis.

**LYME DISEASE**

**Definition**
Multisystem disease caused by a spirochete (*Borrelia burgdorferi*) transmitted by the bite of an *Ixodes* tick (most commonly belonging to the species *scapularis*).

**Diagnosis**

**H&P**
The clinical manifestations vary w/stage of disease:
- Stage I (localized early infection): usually manifested by a characteristic expanding annular skin lesion (ECM); it typically occurs 3-30 days after the tick bite as a centrifugally expanding, erythematous annular patch giving a bull’s-eye appearance.
- Stage II (disseminated infection): follows stage I by days or weeks; pts may experience attacks of joint swelling and pain in large joints, neurologic complications (aseptic meningitis, encephalitis, cranial neuritis), cardiac abnormalities (AV block, myocarditis), and various other multisystem manifestations.
- Stage III (persistent infection): follows stage II by 1 or more years and is manifested by inflammatory arthritis affecting large joints (particularly the knee) and chronic cutaneous and neurologic sequelae; chronic Lyme arthritis is associated w/HLA-DR4 and HLA-DR2 alleles.

**Labs**
- Serologic tests w/ELISA should be used only to support a clinical dx, not as the primary basis for making diagnostic or treatment decisions. False – results may be seen in the initial 2-4 wk of infection and may be caused by early treatment of ECM; false + can occur w/other spirochetal infections and in pts w/Various autoimmune disorders (e.g., SLE, RA). Western blot is used to confirm dx.

**Treatment**
- Doxycycline 100 mg bid or amoxicillin 500 mg tid × 14 days (doxycycline should be avoided in children and pregnant women). A single 200-mg dose of doxycycline given within 72 hr after an *I. scapularis* tick bite has been reported effective in preventing the development of Lyme disease.
- Alternative treatments: cefuroxime axetil 500 mg bid for 14-21 days, erythromycin 250 mg qid for 14 days, azithromycin 500 mg PO × 7-10 days
- Early disseminated and late persistent infection: 30 days of treatment necessary. Doxycycline and ceftriaxone appear equally effective for acute disseminated Lyme disease.
- Arthritis: 30 days of doxycycline or amoxicillin. Alternative is IV ceftriaxone 2 g/day for 14-28 days.
- Neurologic involvement requires parenteral abx: ceftriaxone 2 g/day for 21-28 days; alternative: cefotaxime 2 g q8h; alternative: PCN G 5 million U qid
- Cardiac involvement: IV ceftriaxone or IV cefotaxime or PCN

**LYMPHOGRANULOMA VENEREUM**

**Definition**
STD caused by *Chlamydia trachomatis*. 
Diagnosis

H&P

- Primary stage:
  - Papule, shallow ulcer
  - Herpetiform lesion at site of inoculation (most common)
  - Incubation period: 3-21 days
  - Most common site of lesion in women: posterior wall, fourchette, or vulva
  - Spontaneous healing, w/o scarring
- Second stage:
  - Inguinal syndrome: characteristic inguinal adenopathy 1-4 wk after primary lesion in 70% of cases
  - Sx: painful, extensive adenitis (bubo) and suppurative may occur w/numerous sinus tracks
  - Groove sign signaling femoral and inguinal node involvement (20%); most often seen in men
  - Involvement of deep iliac and retroperitoneal lymph nodes in women may present as a pelvic mass.
- Third stage (anogenital syndrome):
  - Subacute:
  - Late: tissue destruction or scarring, sinuses, abscesses, fistulas, strictures of perineum, elephantiasis

Labs

- Complement fixation test: titer >1:64 in active infection
- Cell culture of *Chlamydia*: aspiration of fluctuant node yields highest rates of recovery
- CBC: mild leukocytosis w/lymphocytosis or monocytosis
- VDRL, HIV to r/o other STDs

Treatment

- Doxycycline 100 mg PO bid × 21 days
- Erythromycin base 500 mg PO qid × 21 days
- Sulfisoxazole 500 mg PO qid × 21 days
- Surgical:
  - Aspirate fluctuant nodes
  - I&D abscesses

253 MELANOMA

Definition

Skin neoplasm arising from the malignant degeneration of melanocytes. It is classically subdivided into four types:

- Superficial spreading melanoma (70%)
- Nodular melanoma (15%-20%)
- Lentigo maligna melanoma (5%-10%)
- Acral lentiginous melanoma (7%-10%)

Diagnosis

H&P

- **Superficial spreading melanoma** is most often found on the lower legs, arms, and upper back. It may have a combination of many colors or may be uniformly brown or black.
- **Nodular melanoma** can be found anywhere on the body, but it most frequently occurs on the trunk on sun-exposed areas. It has a dark-brown or red-brown appearance, can be dome shaped or pedunculated; it is frequently misdiagnosed because it may resemble a blood blister or hemangioma and may also be amelanotic.
- **Lentigo maligna melanoma** is generally found in older adults in areas continually exposed to the sun and frequently arising from lentigo maligna (Hutchinson’s freckle) or melanoma in situ. It might have a complex pattern and variable shape; color is more uniform than in superficial spreading melanoma.
- **Acral lentiginous melanoma** frequently occurs in soles, subungual mucous membranes, and palms (sole of the foot is the most prevalent site). Unlike other types of melanoma, it has a similar incidence in all ethnic groups.
The warning signs that the lesion may be a melanoma can be summarized w/the ABCDE rules:

- A: Asymmetry (e.g., lesion is bisected and halves are not identical)
- B: Border irregularity (uneven, ragged border)
- C: Color variegation (presence of various shades of pigmentation)
- D: Diameter enlargement (>6 mm)
- E: Evolving (i.e., lesions that have changed over time).

**Labs**

- Perform excisional bx w/elliptical excision that includes 1-2 mm of nl skin surrounding the lesion and extends to the SC tissue; incisional punch bx is sometimes necessary in surgically sensitive areas (e.g., digits, nose).
- The sentinel lymph node dissection (SLND) should be considered in pts w/intermediate (1- to 4-mm) melanomas or high-risk skin tumors to obtain information about a pt’s subclinical lymph node status w/min. morbidity. It involves the use of radiologic lymphoscintigraphy to map lymphatic drainage from the site of the primary melanoma to the first “sentinel” lymph node in the region. When it is properly performed, if the sentinel node is negative, the remaining lymph nodes in the region will not have mets in more than 98% of cases. The staging of intermediate-thickness (1.2- to 3.5-mm) primary melanomas, according to the results of sentinel node bx, provides important prognostic information and identifies pts w/nodal mets whose survival can be prolonged by immediate lymphadenectomy.

**Pathology Report**

The pathology report should indicate the following:

- Tumor thickness (Breslow microstage)
- Tumor depth (Clark level): the depth of invasion is the most important histologic prognostic parameter in evaluating the primary tumor.
- Mitotic rate: tabulated as mitosis/mm² in the dermal part of the tumor in which most mitoses are identified.
- Radial growth rate vs. vertical growth rate: radial growth phase describes the growth of melanoma within the epidermis and along the dermal-epidermal junction.
- Tumor-infiltrating lymphocytes: they have a strong predictive value in vertical growth phase melanomas and are defined as brisk, nonbrisk, and absent.
- Histologic regression: characterized by the absence of melanoma in the epidermis and dermis flanked on one or both sides by melanoma.
- Reverse transcriptase–PCR (RT-PCR) assay for tyrosine messenger RNA is a useful marker for the presence of melanoma cells. It is performed on sentinel lymph node bx specimen and is useful for detection of submicroscopic mets.

**Etiology**

- UV light is the most important cause of malignant melanoma.
- There is a modest ↑ in melanoma risk in pts w/small nondysplastic nevi and a much greater risk in those w/dysplastic lesions.
- The CDKN2A gene, residing at the 9p21 locus, is often deleted in pts w/familial melanoma.

**Treatment**

- Initial excision of the melanoma
- Re-excision of the involved area after histologic dx:
  - The margins of re-excision depend on the thickness of the tumor.
  - Low-risk or intermediate-risk tumors require excision of 1-3 cm.
  - Melanomas of moderate thickness (0.9-2.0 mm) can be excised safely w/2-cm margins.
  - A 1-cm margin of excision for melanoma w/poor prognosis (as defined by a tumor thickness of at least 2 mm) is associated w/significantly ↑ risk of regional recurrence than is a 3-cm margin, but w/similar overall survival rate.
- Lymph node dissection: recommended in all pts w/enlarged lymph nodes. Lymph node evaluation is important in pts w/melanoma 1 mm in depth because it determines the overall prognosis and need for therapeutic lymph node dissection or adjuvant treatment.
• Elective lymph node dissection remains controversial.
• It is indicated w/positive sentinel node. It may be considered in those w/ primary melanoma that is between 1 and 4 mm thick (especially in pts <60 yr of age).
• Adjuvant Rx w/interferon alfa-2b (intron A) in pts w/metastatic melanoma is approved by the FDA for AJCC stages IIb and III melanoma; however, its statistical benefit remains unclear.
• Dacarbazine (DTIC) and interleukin-2 can be used in metastatic melanoma. Results are generally poor, w/median survival in pts w/distant metastatic melanoma approximately 6 mo.
• Combinations of dacarbazine and cisplatin w/interleukin-2 and interferon alfa (biochemotherapy)
• Novel therapeutics involve cancer vaccines and use of granulocyte-macrophage colony-stimulating factor (GM-CSF) and angiogenesis inhibitors.

**Clinical Pearls**

- Prognosis varies w/the stage of the melanoma. The 5-yr survival related to thickness is as follows: <0.6 mm, 99% survival; <0.6-1.49 mm, 85%; 1.5-2.49 mm, 84%; 2.5-3.9 mm, 70%; >4 mm, 44%.
- The 5-yr survival in pts w/distant metastasis is <10%.

## 254 MENINGITIS, ASEPTIC (VIRAL)

### Diagnosis

**H&P**
- Fever
- Headache
- Nuchal rigidity
- Photophobia
- Myalgias
- Vomiting
- Rash

**Labs**
- CSF exam:
  - Pleocytosis
  - Lymphocytic predominance (neutrophils in early stages)
  - Opening pressure: 200-250 mm Hg
  - WBC: 100-1000 mm$^3$
  - ↑ CSF protein
  - ↓/N CSF glucose
  - Negative Gram stain, cultures, CIE, latex agglutination
  - Viral cultures or serologic testing may be diagnostic.
  - PCR for HSV, West Nile, or enterovirus

**Imaging**
- CT scan or MRI: if cerebral edema, focal neurologic findings develop

### Etiology
- Enterovirus
- Mumps virus
- Measles
- Arboviruses
- Herpes (simplex and zoster)
- HIV
- Lymphocytic choriomeningitis virus
- Adenovirus
- CMV
- Arthropod-borne viruses
- West Nile virus

### Treatment
- Rx is supportive unless HSV is detected, which would be treated w/IV acyclovir.
Clinical Pearl
- Enteroviruses are the most common cause of viral meningitis and are transmitted by the fecal-oral and less commonly by the respiratory route.

255 Meningitis, Bacterial

Definition
Inflammation of the meninges secondary to bacterial infection.

Diagnosis

H&P
- Classic presentation consists of fever, headache, lethargy, confusion, and nuchal rigidity; these manifestations are not always present, particularly in infants, elderly, and immunocompromised pts.
- Kernig’s sign: pain in the lower back or posterior thigh when the knee is extended while the pt is lying in the supine position and the hip is flexed at a right angle.
- Brudzinski’s sign: rapid flexion of the neck elicits involuntary flexing of the knees in a supine position.
- ΔMS (confusion, lethargy)
- Bulging fontanelle, poor feeding, vomiting, and respiratory distress in infants
- Petechial-purpuric rash that develops on the trunk, LEs, mucous membranes, conjunctiva, and occasionally the palms and soles is suggestive of meningococcal meningitis but can also be present in viral meningitis and other bacterial meningitis.
- Papilledema: unusual and should raise the suspicion of brain abscess or mass lesion.
- Seizures (up to 40% of pts in the first week of illness); cranial nerve palsies (most notably sensorineural hearing loss) may also be present early in the course of illness.

Labs
- WBC usually reveals leukocytosis w/shift to the left; however, leukopenia can also be present; peripheral lymphocytosis is usually suggestive of a viral cause (aseptic meningitis).
- Blood cultures (abx Rx should not be delayed until all cultures are obtained if pt is very ill)
- LP: CSF exam
  - Opening pressure >100-200 mm Hg
  - WBC <5 to >100 mm^3
  - Neutrophilic predominance: >80%
  - Gram stain of CSF: + in 60%-90%
  - CSF protein: >50 mg/dL
  - CSF glucose: <40 mg/dL
  - Culture: positive in 65%-90% cases
  - CSF bacterial antigen: 50%-100% sensitivity
  - E-test for susceptibility of pneumococcal isolates

Etiology
- S. pneumoniae: adults and elderly pts; predisposing factors include blunt head trauma, otitis media, pneumonia, sickle cell disease, and CSF leaks; mortality rate is 30%; permanent neurologic sequelae occur in 50% of survivors.
- N. meningitidis: young adults and children, especially those w/complement deficiencies
- H. influenzae: preschool-age children; predisposing factors in adults include head trauma, otitis media, and sinusitis.
- L. monocytogenes: elderly and immunosuppressed pts (lymphoma, corticosteroids, dialysis pts, organ transplant recipients)
- Gram-negative bacilli: neonates (acquired in passage through birth canal), elderly debilitated pts, neutropenic pts, and in postcranial surgery
- S. aureus: diabetic pts and pts w/S. aureus pneumonia or cancer

Treatment
- Empiric IV abx treatment pending Gram stain and culture results
- Neonates: ampicillin + cefotaxime
Infants and children: third-generation ceph (cefotaxime 2g IV q4h or ceftriaxone 2g IV q12h) plus vancomycin (25-50 mg/kg/day)
Adults (18-50 yr): third-generation ceph plus vancomycin
Older adults (>50 yr): ampicillin (2 g IV q4h) + third-generation ceph plus vancomycin
Suspected PCN-resistant pneumococcus: ceftriaxone or cefotaxime plus vancomycin
Steroids: dexamethasone 0.15 mg/kg q6h for first 4 days of Rx in adults w/bacterial meningitis and ΔMS or acute neurologic phenomenon. Dexamethasone also benefits children w/Hib meningitis (reduced hearing loss) and should be given within the first 2 days of illness.

256 MESENTERIC ADENITIS

Definition
Syndrome of acute RLQ abd pain associated w/mesenteric lymph node enlargement and a nl appendix.

Diagnosis
H&P
- Abd pain of variable severity (mild ache to severe colic) beginning in upper abd or RLQ eventually localizes in right side but not in a precise location (unlike appendicitis).
- In Yersinia infection outbreaks, the sx include abd pain (84%), diarrhea (78%), fever (43%), anorexia (22%), nausea (13%), and vomiting (8%).
- PE:
  - Other lymphadenopathy (20% of cases)
  - RLQ tenderness (site of max tenderness may vary from one exam to the next)
  - Guarding (rare)
  - Mild fever

Labs
- CBC: leukocytosis
- Laparotomy if appendicitis is suspected. In general, dx is made on exploration of the abd of a pt suspected of having acute appendicitis. On lap, appendix appears nl, and enlarged mesenteric lymph nodes are noted. Excision of an enlarged lymph node w/culture and nodal histology may provide information about the etiology but is not routinely employed.

Imaging
- CT abd and pelvis

Etiology
- Reactive hyperplasia of lymph nodes that drain the ileocecal region due to Yersinia enterocolitica, Yersinia pseudotuberculosis, Salmonella species, E. coli, and streptococci

Treatment
- Recurrent bouts are common; therefore, if laparotomy is performed and a nl appendix is found, it should be removed.

257 MESENTERIC ISCHEMIA

Definition
Sudden onset of intestinal hypoperfusion caused by emboli, arterial or venous thrombosis, or vasoconstriction resulting from low-flow states.

Diagnosis
H&P
- The classic presentation: pt w/risk factors, exhibiting the rapid onset of severe periumbilical pain out of proportion to PE findings
- N/V
- Initial abd exam may be nl, w/no rebound or guarding, or show min. distention or OB + stool.
- Later in the course, the pt may present w/gross distention, absence of bowel sounds, and peritoneal signs. In the elderly, ΔMS may be found.
**Labs**
- Labs are nonspecific early in the course. Later they reveal leukocytosis, acidosis, and ↑ Hct (from hemoconcentration).
- Proteins C and S, antithrombin III, factor V (Leiden) when hypercoagulable state is suspected

**Imaging**
- With strong clinical suspicion, w/u should proceed directly to angiography, w/o delay for CT scan or other testing. Mesenteric angiography is gold standard.
- Plain films: nl 25% of the time in the early stages. Suggestive findings may include ileus, bowel wall thickening, and intramural gas.
- Doppler U/S evaluation of intestinal blood flow: often limited by air-filled loops of bowel
- CT scan: nonspecific. Portal venous gas or intramural gas may be seen after the development of gangrene. CT scan is more useful in cases of mesenteric vein thrombosis causing acute mesenteric ischemia (90% sensitivity).
- MRA may prove to be useful, but data comparing this with angiography are needed.

**Etiology**
- Mesenteric arterial embolism: typically from the left atrium, LV, or cardiac valves. The superior mesenteric artery is most commonly affected.
- Mesenteric arterial thrombosis: often in pts w/prior progressive atherosclerotic stenoses, w/superimposed abd trauma or infection
- Mesenteric venous thrombosis: may occur in the setting of hypercoagulable states (acquired or inherited), blunt trauma, abd infection, portal HTN, pancreatitis, and portal malignant neoplasm.
- Nonocclusive mesenteric ischemia: usually occurs in the setting of atherosclerotic vascular disease, often in pt w/acute CVD process who is being treated w/drugs that ↓ intestinal perfusion. This may include pts w/recent cardiac surgery and dialysis pts. Cocaine use has also been a causative factor in a number of cases.

**Treatment**
- Goal is to restore blood flow as rapidly as possible to ischemic bowel, before the occurrence of infarction.
- Rx varies according to etiology.
- If signs of peritonitis: laparotomy and resection of infarcted bowel
- Superior mesenteric artery embolus: embolectomy. Depending on the location and degree of occlusion of the embolus, surgical revascularization, intra-arterial infusion of thrombolytics or vasodilators, or systemic anticoagulation may be considered.
- Superior mesenteric artery thrombosis: emergency surgical revascularization
- Mesenteric venous thrombosis: Rx depends on the presence or absence of peritoneal signs. Laparotomy and resection of infarcted bowel in more advanced cases; or if there are no peritoneal signs, anticoagulant Rx w/heparin.
- Correction of acidosis, administration of broad-spectrum abx, and gastric decompression by NG tube

**Clinical Pearls**
- Prognosis is best in acute mesenteric ischemia resulting from mesenteric venous thrombosis and after surgical treatment of acute arterial embolism. It remains poor in cases of arterial thrombosis and nonocclusive ischemia.
- With delayed dx, intestinal infarction, resulting in perforation or gangrenous bowel, sepsis, shock, and death, is typical.

### MESENTERIC VENOUS THROMBOSIS

**Definition**
Thrombotic occlusion of the mesenteric venous system involving major trunks or smaller branches and leading to intestinal infarction in its acute form.
**Microscopic Polyangiitis**

**Definition**
Subgroup of polyarteritis nodosa, distinguished by the presence of segmental necrotizing GN and histologic involvement of arterioles, capillaries, venules, and rarely medium-sized arteries.

**Diagnosis**
**H&P**
- Renal disease (100%), fever (60%), arthralgias (50%), purpura (40%), pulmonary disease (hemorrhage, infiltrates, effusion; 50%)

**Labs**
- Necrotizing pauci-immune GN, pulmonary capillaritis, leukocytoclastic vasculitis

**Treatment**
- Prednisone 1 mg/kg/day
- Cyclophosphamide 2.5 mg/kg/day

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**Chapter 3 Diseases and Disorders**

**Diagnosis**
**H&P**
- Sx: abd pain (90%), typically out of proportion to the physical findings;
- N/V (50%), GI bleeding (50% occult, 15% gross)
- Early: abd tenderness, ↓ bowel sounds, abd distention
- Later: guarding and rebound tenderness, fever, and septic shock

**Labs**
- CBC (leukocytosis), electrolytes (metabolic acidosis [lactic] indicates bowel infarction), ↑ amylase

**Imaging**
- Abd CT (diagnostic in 90%): bowel wall thickening, venous dilation, venous thrombus

**Etiology**
- Hypercoagulable states
- Portal HTN
- Inflammation
  - Pancreatitis
  - Peritonitis (e.g., appendicitis, diverticulitis, perforated viscus)
  - IBD
  - Pelvic or intra-abd abscess
- Intra-abd cancer
- Postop state or trauma
  - Blunt abd trauma
  - Postop states (abd surgery)
- Thrombosis may begin in small mesenteric branches (e.g., in hypercoagulable states) and propagate to the major venous mesenteric trunks or begin in large veins (e.g., in cirrhosis, intra-abd cancer, surgery) and extend distally. If collateral drainage is inadequate, the intestine becomes congested, edematous, cyanotic, and hemorrhagic and eventually may infarct.

**Treatment**
- Anticoagulation or thrombolytic Rx
- Laparotomy if intestinal infarction is suspected
  - Short ischemic segment: resection
  - Long ischemic segment:
    - Nonviable: resection or close
    - Viable: intra-arterial papaverine or thrombectomy followed by “second-look” intervention

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**Mitrail Regurgitation (MR)**

**Definition**
Retrograde blood flow through the left atrium secondary to an incompetent mitral valve. Eventually there is an ↑ in left atrial and pulmonary pressures, which may result in right ventricular failure.
Diseases

**Diagnosis**

**H&P**

- Hyperdynamic apex, often w/palpable left ventricular lift and apical thrill
- Holosystolic murmur at apex w/radiation to base or to left axilla; poor correlation between the intensity of the systolic murmur and the degree of regurgitation
- Apical early- to mid-diastolic rumble (rare)

**Imaging**

- Echo: enlarged left atrium, hyperdynamic LV (erratic motion of the leaflet is seen in pts w/ruptured chordae tendineae); Doppler echo will show evidence of MR.

**Etiology**

- Papillary muscle dysfunction (as a result of ischemic heart disease)
- Ruptured chordae tendineae
- Infective endocarditis
- Calcified mitral valve annulus
- Left ventricular dilation
- Rheumatic valvulitis
- Primary or secondary MVP
- Hypertrophic cardiomyopathy
- Idiopathic myxomatous degeneration of the mitral valve
- Myxoma
- SLE
- Fenfluramine, dexfenfluramine

**Treatment**

- Medical
  - Afterload reduction (to ↓ regurgitant fraction and ↑ CO): amlodipine, nifedipine, ACEs, hydralazine plus nitrates
- Surgery
  - Early intervention in symptomatic pts despite optimal medical Rx and in pts w/moderate to severe MR and min. sx if there is echo evidence of rapidly progressive ↑ in LV end-diastolic and end-systolic dimension (echo evidence of systolic failure includes end-systolic dimension >55 mm and fractional shortening <31%).
  - Surgery is also indicated in asymptomatic pts if there is evidence of pulmonary HTN or recent AF. Quantitative grading of MR is a powerful predictor of the clinical outcome of asymptomatic MR. In general, pts w/regurgitant orifices of ≤40 mm² should be considered for prompt surgery, whereas those w/orifices between 20 and 39 mm² can be observed closely.

**261 MITRAL STENOSIS**

**Definition**

Narrowing of the mitral valve orifice. The cross section of a nl orifice measures 4–6 cm². A murmur becomes audible when the valve orifice becomes <2 cm². When the orifice approaches 1 cm², the condition becomes critical and sx become more evident.

**Diagnosis**

**H&P**

- Prominent jugular A waves
- Opening snap in early diastole; short (<0.07 second) A₂ to opening snap interval indicates severe mitral stenosis.
- Apical mid-diastolic or presystolic rumble that does not radiate
- Accentuated S₁ (because of delayed and forceful closure of the valve)
- If pulmonary HTN is present, there may be an accentuated P₂ or a soft, early diastolic decrescendo murmur (Graham Steel murmur) due to pulmonary regurgitation (best heard along LSB, may be confused w/Al).
- Palpable right ventricular heave at LSB
- Sx of left-sided CHF: dyspnea on exertion, PND, orthopnea
- Right ventricular dysfunction (in late stages): peripheral edema, enlarged and pulsatile liver, ascites


**Imaging**
- Echo: the characteristic finding on echocardiography is a markedly diminished E to F slope of the anterior mitral valve leaflet during diastole; there is also fusion of the commissures, resulting in anterior movement of the posterior mitral valve leaflet during diastole (calcification in the valve may also be noted).

**Etiology**
- Progressive fibrosis, scarring, and calcification of the valve
- Rheumatic fever (still a common cause in underdeveloped countries); heart valves most frequently affected in rheumatic heart disease (in descending order of occurrence): mitral, aortic, tricuspid, and pulmonary
- Congenital defect (parachute valve)
- Rare causes: endomyocardial fibroelastosis, malignant carcinoid syndrome, SLE

**Treatment**
- Medical:
  - AF: diltiazem, digoxin, or esmolol. IV diltiazem or esmolol is preferred when a rapid ↓ in HR is required.
  - CHF: diuretics and sodium restriction
- Surgical: valve replacement when valve orifice is <0.7 cm² or if sx persist despite optimal medical Rx
- Consider valve commissurotomy if valve is noncalcified and if there is pure mitral stenosis w/o significant subvalvular disease.
- Percutaneous transvenous mitral valvotomy: useful in pts w/mitral stenosis responding poorly to medical Rx, who are poor surgical candidates, and whose valve is not heavily calcified

### 262 MITRAL VALVE PROLAPSE (MVP)

**Definition**
Posterior bulging of interior and posterior leaflets in systole. MVP syndrome refers to a constellation of MVP and associated sx (e.g., autonomic dysfunction, palpitations) or other physical abnormalities (e.g., pectus excavatum).

**Diagnosis**

**H&P**
- Usually, young female pt w/narrow AP chest diameter, low BW, low BP
- Mid to late click, heard best at the apex
- Crescendo mid to late diastolic murmur
- Findings accentuated in the standing position
- Most pts asymptomatic; sx (if present): chest pain, palpitations
- Neuro abnormalities (e.g., TIA or stroke) rare

**Imaging**
- Echo: anterior and posterior leaflets bulging posteriorly in systole

**Etiology**
- Myxomatous degeneration of connective tissue of mitral valve
- Congenital deformity of mitral valve and supportive structures
- Secondary to other disorders (e.g., Ehlers-Danlos, pseudoxanthoma elasticum)

**Treatment**
- β-Blockers (↓ HR = ↓ stretch on prolapsing valve leaflets); useful in symptomatic pts (e.g., palpitations, chest pain). Valve replacement or valve repair indicated in severe mitral regurgitation due to MVP.

**Clinical Pearl**
- Incidence of complications of MVP is <1%/yr; generally associated w/↑ in mitral leaflet thickness to ≥5 mm.

### 263 MIXED CONNECTIVE TISSUE DISEASE (MCTD)

**Definition**
Set of connective tissue sx that sometimes overlap w/other known connective tissue diseases (SLE, progressive systemic sclerosis, polymyositis). The disorder is also known as overlap syndrome or undifferentiated connective tissue disease.
Chapter 3  Diseases and Disorders

Diagnosis

H&P
- Polyarthitis, polyarthralgia
- RP, hand swelling, or sclerodactyly
- Esophageal hypomotility, myalgia, and muscle weakness
- Other: pericarditis, facial erythema, pulmonary involvement, psychosis

Labs
- + ANA (often speckled pattern)
- ↑ ESR
- RF is often present in low titers.
- ↑ CPK if myositis is present
- Anti-RNP Ab may be present.

Treatment
- Corticosteroids
- NSAIDs
- Immunosuppressive agents

264 MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE (MGUS)

Definition
Disorder characterized by a serum M protein concentration <3 g/dL, <10% plasma cells in the bone marrow, absence of anemia, renal insufficiency, hypercalcemia, or bone lesions. M protein may be absent in the urine or present in small amounts.

Diagnosis
- Currently, no single test can distinguish MGUS from MM.
- The time interval from the initial dx of MGUS to progression to a more serious disorder ranges from 2-29 yr (median, 10 yr).
- The risk of progression is related to the level of M protein values and to the type of protein (↑ risk w/higher M protein values and in pts w/IgM and IgA M proteins).
- Monitor serum M protein:
  - If serum M protein is <2 g/dL, repeat electrophoresis after 6 mo; if stable, repeat annually.
  - If serum M protein is >2 g/dL, repeat electrophoresis every 6 mo.

265 MUCORMYCOSIS

Definition
Fungal infection by Zygomycetes fungi.

Diagnosis

H&P
- Rhinocerebral–rhino-orbital–paranasal syndrome: fever, facial and orbital pain, headache, diplopia, loss of vision, facial or orbital cellulitis, facial anesthesia, cranial nerve dysfunction, black nasal d/c, epistaxis, and seizure. Thrombosis of the cavernous sinus or internal carotid artery may occur. It is found most commonly in diabetics, primarily in the presence of acidosis, and in pts w/leukemia and neutropenia.
- Pulmonary mucormycosis: pneumonia, lung abscess, pulmonary infarction, pleurisy, pleural effusion, hemoptysis, chills, and fever. It is found most commonly in immunocompromised neutropenic hosts after chemotherapy for hematologic malignant neoplasms.
- GI zygomycosis: abd pain, diarrhea, GI hemorrhage, ulcers, peritonitis, and bowel infarction. It is found most commonly in pts w/extreme malnutrition.
- Cutaneous zygomycosis: manifested as nodular lesions (hematogenous seeding) or a wound infection. It involves primarily the epidermis and dermis after use of occlusive dressings that have not been properly sterilized.
- Brain abscess occurs most often from extension of the fungus from the nose or paranasal sinuses through adjacent bones in severely debilitated pts.
**Labs**
- Bx of infected tissue w/direct light microscopy exam. The fungi typically appear as broad (10-20 µm in diameter) nonseptate hyphae w/branches occurring at right angles.
- BAL or bronchoscopy w/bx for smear, culture, and histologic examination

**Treatment**
- Amphotericin B given IV at a daily dose of 1.0-1.5 mg/kg infused during 2-4 hr for a total of 1-4 g
- Lipid preparations of amphotericin B may be less toxic (i.e., amphotericin B lipid complex, amphotericin B colloidal dispersion, and liposomal amphotericin B).
- The role of flucytosine, rifampin, and tetracycline is controversial.
- Surgical débridement or radical resection

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**MULTIFOCAL ATRIAL TACHYCARDIA**

**Definition**
Chaotic, irregular atrial activity at rates of 100-180 bpm.

**Diagnosis**
ECG (Fig. 3-38):
- Variable P-P intervals
- Morphology of the P wave varies from beat to beat, w/min. of 3 different forms of P wave besides those from the sinus node.
- Each QRS complex is preceded by a P wave.
- Atrial rate of 100-150 bpm

![Figure 3-38](image)

**FIGURE 3-38.** Multifocal atrial tachycardia. Letter designations A1, A2, A3, and A4 show premature contractions from varying foci. Notice that the fourth, eighth, and eleventh QRS complexes are aberrant.

**Etiology**
- COPD
- Metabolic disturbances (hypoxemia, hypokalemia, hypomagnesemia)
- Sepsis
- Theophylline toxicity
- CHF
- Acute MI

**Treatment**
- Treat underlying cause (e.g., improve oxygenation, correct electrolyte abnormalities).
- Verapamil 5 mg IV at a rate of up to 1 mg/min (may repeat after 20 min). Ca gluconate, 1 g IV given 5 min before treatment w/verapamil, may ↓ drug-induced hypotension w/o affecting the antiarrhythmic effect.
- Metoprolol or esmolol used in absence of COPD, CHF, or bronchospasm
- Amiodarone useful in refractory cases

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**MULTIPLE ENDOCRINE NEOPLASIA (MEN)**

**Definition**
The syndrome of MEN occurs familially in an autosomal dominant pattern. The endocrine “neoplasms” may be expressed as hyperplasia, adenoma, or carcinoma and may develop synchronously or metachronously.

**Classification**

**MEN I (Werner’s Syndrome)**
- Tumors or hyperplasia of anterior pituitary, enteropancreatic neuroendocrine system (insulinoma, gastrinoma, glucagonoma), parathyroid, and other tissues
Chapter 3 Diseases and Disorders

MULTIPLE MYELOMA

Definition
Malignant neoplasm of plasma cells characterized by overproduction of intact monoclonal immunoglobulin or free monoclonal κ or λ chains. Diagnostic criteria require the following:
- Presence of ≥10% plasma cells in bone marrow (or bx of a tissue w/monoclonal plasma cells)
- Monoclonal protein in serum or urine. Pts w/o detectable monoclonal protein are considered to have nonsecretory myeloma.
- Evidence of end-organ damage (Ca elevation, renal insufficiency, anemia, or bone lesions [CRAB])

Diagnosis

H&P
- Bone pain (58%) (back, thorax) or pathologic Fxs (30%): due to osteolytic lesions
- Fatigue (32%) or weakness: due to anemia secondary to bone marrow infiltration w/plasma cells
- Recurrent infections: due to impaired neutrophil function and deficiency of nl immunoglobulins
- N/V: due to constipation and uremia
- Delirium: due to hypercalcemia
- Neurologic complications: spinal cord or nerve root compression, blurred vision from hyperviscosity

Possible associated conditions:
- Adrenocortical adenoma or hyperplasia
- Thyroid adenoma or hyperplasia
- Renal cortical adenoma
- Carcinoid tumors
- GI polyps
- Skin angiofibromas and skin collagenomas

Clinical manifestations:
- Peptic ulcer and its complications
- Hypoglycemia
- Hypercalcemia or nephrocalcinosis
- Headache, visual field defects, secondary amenorrhea
- Multiple SC lipomas
- Other: flushing, acromegaly, Cushing’s syndrome, hyperthyroidism

MEN II (Sipple’s Syndrome, MEN IIA)
- Associated w/MTC, pheochromocytoma, and hyperparathyroidism

Clinical manifestations:
- Neck mass (caused by MTC)
- HTN
- Headache, palpitations, sweating
- Hypercalcemia, nephrocalcinosis, osteitis fibrosa cystica

Relatives of affected persons should be screened to detect medullary carcinoma at an early stage; screening can be accomplished with
- Pentagastrin test: unreliable because it does not distinguish C-cell hyperplasia from small carcinomas
- DNA analysis: reliable method for identification of MEN IIA gene carriers

MEN III (Multiple Mucosal Neuroma Syndrome, MEN IIB)
- Associated w/MTC, pheochromocytoma, and multiple mucosal neuromas
- Possible associated conditions: intestinal ganglioneuromatosis, marfanoid habitus

Clinical manifestations:
- Neck mass (caused by MTC)
- HTN
- Headache, palpitations, sweating, HTN
- Mucosal neuromas (initially noted as whitish, yellow-pink nodules involving lips and anterior third of tongue)
- Marfan-like habitus (w/absence of CV abnormalities and lens subluxation)
- Peripheral neuropathy (caused by neuromatous plaques overlying the posterior columns of the spinal cord, cauda equina, and sciatic nerve)
Diseases

MÚLTIPLE MYELOMA

Chapter 3

Labs

- Normochromic, normocytic anemia; rouleaux formation on peripheral smear
- Hypercalcemia (15% of pts at dx)
- ↑ BUN, Cr, uric acid, and total protein
- Proteinuria secondary to overproduction and secretion of free monoclonal k or λ chains (Bence Jones protein).
- Tall homogeneous monoclonal spike (M spike) on protein IEP (75% of pts); ↓ nl immunoglobulins
- The ↑ immunoglobulins are generally IgG (75%) or IgA (15%).
- Approximately 17% of pts have flat level of immunoglobulins but ↑ light chains in the urine by electrophoresis.
- A very small percentage (<2%) of pts have nonsecreting myeloma (no ↑ in immunoglobulins and no light chains in the urine) but have other evidence of the disease (e.g., bone marrow exam).
- ↓ anion gap resulting from the + charge of the M proteins and the frequent presence of hyperatremia in myeloma pts
- Hyponatremia, serum hyperviscosity (more common w/production of IgA)
- Bone marrow exam: nests or sheets of plasma cells >30% of the bone marrow, and ≥10% are immature
- Serum β₂-microglobulin: >8 mg/L indicates high tumor mass and aggressive disease.
- ↑ LDH at dx indicates poorer prognosis.
- ↑ Serum interleukin-6
- FISH: high-risk pts have FISH deletion 17p, FISH translocation 4;14, FISH translocation 14;16, cytogenetic deletion 13q, cytogenetic hypodiploidy.

Imaging

- X-ray films of painful areas: punched-out lytic lesions
- MRI: for suspected spinal compression or soft tissue plasmacytomas
- Bone scans not useful because lesions are not blastic

Treatment

- Autologous SCT
- Induction Rx in pts ineligible for transplantation:
  - Thalidomide in combination w/melphalan and prednisone
  - Melphalan and prednisone: the rates of response to this treatment range from 40%-60%.
  - Vincristine, doxorubicin, and dexamethasone (VAD) can be used in pts not responding to or relapsing after treatment w/melphalan and prednisone; methylprednisolone is substituted for dexamethasone (VAMP) in some centers.
- Rx for relapsed and refractory myeloma:
  - If the relapse occurs longer than 6 mo after conventional Rx is stopped, the initial chemotherapy regimen can be reinstituted.
  - Consider autologous stem cell transplantation as salvage Rx in pts who had stem cell cryopreserved early in the course of the disease.
  - Chemotherapy w/vincristine, doxorubicin, and dexamethasone
  - Thalidomide or lenalidomide useful to induce responses in pts w/MM refractory to chemotherapy
  - Bortezomib useful for refractory MM and for pts w/myeloma who are not candidates for hematopoietic stem cell transplantation
- Prompt dx and Rx of infections. Common bacterial agents are S. pneumoniae and H. influenzae. Prophylaxis against Pneumocystis w/TMP-SMZ in pts receiving chemotherapy and high-dose corticosteroid regimens.
- Vaccinate against S. pneumoniae, influenza, and H. influenzae
- Rx hypercalcemia w/IV fluids, corticosteroids, bisphosphonates (pamidronate, zoledronate)
- Pain management w/analgescics; RT for painful bone lesions or cord compression. Surgical stabilization of pathologic Fx. Consider vertebroplasty or kyphoplasty for selected vertebral lesions.
- Rx severe anemia w/erythropoietin
## MULTIPLE SCLEROSIS (MS)

### Definition

Chronic autoimmune demyelinating disease of the CNS characterized by clinical attacks (relapses) correlated w/lesions separated in time and space. A relapse is the subacute onset of neurologic dysfunction that lasts for at least 24 hr. Subtypes of MS include relapsing-remitting MS (RRMS), relapses followed by complete or nearly complete recovery; secondary progressive MS (SPMS), progression of disability w/few or no relapses; and primary progressive MS (PPMS), progression from onset. Rare MS variants include Balo’s concentric sclerosis, alternating rings of myelination and demyelination; Marburg’s disease, tumor-like lesion w/significant edema; and Schilder’s diffuse sclerosis, childhood onset w/1-2 large symmetric lesions. Neuromyelitis optica (Devic’s disease) involves primarily the optic nerves and spinal cord and is presently considered a separate disease.

### Diagnosis

**H&P**

- Visual abnormalities
  - Paresis of medial rectus muscle on lateral conjugate gaze (internuclear ophthalmoplegia) and horizontal nystagmus of the adducting eye
  - Central scotoma, ↓ visual acuity (optic neuritis)
  - A Marcus Gunn pupil (pupil that paradoxically dilates w/direct light), indicating damage to the optic nerve anterior to the chiasm, is frequently present.
  - Nystagmus
- Abnormalities of reflexes
  - ↑ DTRs
  - + Hoffmann’s sign, + Babinski
  - ↓ Abd skin reflex, ↓ cremasteric reflex
- *Lhermitte’s sign*: flexion of the neck while the pt is lying down elicits an electrical sensation extending bilaterally down the arms, back, and lower trunk.
- *Uhthoff’s phenomenon*: exercise or heat-induced deterioration of function
- *Charcot’s triad*: nystagmus, scanning speech, and intention tremor
- Impaired recognition of objects by touch alone (astereognosis)

### Specific Diagnosis

- MS: primarily a clinical dx based on a consistent clinical presentation w/evidence of CNS demyelinating lesions disseminated in time and space not better explained by another disease.
- RRMS: h/o two relapses and confirmation on neurologic exam may be sufficient if both support the earlier definition. If there is only one lesion on exam or only one relapse, MRI or other paraclinical testing must be used.
- PPMS: insidious progression of disability for 1 yr w/2 of the following:
  - Brain MRI: 9 T2 lesions in brain or 4 lesions + positive delayed VEP
  - Spine MRI: ≈2 T2 lesions
  - Positive CSF: IgG index or oligoclonal bands

### Imaging

- MRI of brain w/gadolinium: can identify lesions as small as 3-4 mm; used to assess disease load, activity, and progression. MRI reveals multiple, predominantly periventricular plaques; however, nl MRI cannot be used to exclude MS. MRI cervical spine can also be helpful.

### Labs

- LP for all first relapses when the dx of MS is not definite. Possible CSF abnormalities include ↑ protein and mononuclear WBCs (both usually only mild). ↑ CSF IgG index and + oligoclonal bands in 70% and 90%, respectively, of clinically definite MS. False + occur w/IgG index in CNS infections and inflammation but rarely w/oligoclonal bands.
- Serum: CBC, ESR, CRP, CHEM 7, LFTs, ANA, B₁₂, Lyme titer, TSH
- Consider evoked potentials (VEP, SSEP, BAER). Demyelination will slow conduction velocities.
**Treatment**

**Acute General Rx**
- Relapses: high-dose IV methylprednisolone (3-5 days of 1 g MP/day; alternative dose is 15 mg/kg/day), often followed by a 7- to 10-day prednisone taper

**Chronic Rx**
- Disease-modifying Rx for RRMS: interferon beta-1a (IM Avonex, SC Rebif), interferon beta-1b (SC Betaseron), and glatiramer acetate (SC Copaxone). Interferons need CBC and LFT checks (month 1 followed by trimestrally), occasionally TSH; none needed w/glatiramer acetate.
- Monoclonal Ab: natalizumab binds to an α₄ subunit of leukocytes. It is a monthly infusion for RRMS associated w/rare cases of progressive multifocal leukoencephalopathy when used in conjunction w/other immunomodulatory medications.
- Cytotoxic: cyclophosphamide or mitoxantrone for frequent relapses w/rapid disability progression and in early secondary progressive MS. Oral MTX or azathioprine is occasionally used.
- Spasticity: baclofen, tizanidine, diazepam, lorazepam, and intrathecal baclofen (oral medications not tolerated)
- Pain: carbamazepine, gabapentin, pregabalin, or amitriptyline
- Spastic bladder: oxybutynin, tolterodine, or propantheline; prazosin for spastic sphincter
- Fatigue: amantadine 100 mg bid, modafinil (most effective for somnolence), or fluoxetine
- Tremor: clonazepam, carbamazepine, or propranolol

**270 MYASTHENIA GRAVIS (MG)**

**Definition**
Acquired autoimmune disorder of neuromuscular transmission characterized by the presence of a γ-globulin Ab (AChR-Ab) directed against the nicotinic acetylcholine receptor (AChR) of the neuromuscular junction, resulting in reduction in postsynaptic response to ACh.

**Diagnosis**

**H&P**
- The hallmark of MG is weakness made worse w/exercise and improved by rest. Sx fluctuate and are often better in the morning.
- >50% of pts present initially w/ptosis, ocular muscle weakness, or both.
- Difficulty in chewing, abnl smile, dysarthria, dysphagia
- Involvement of the respiratory muscles may require intubation and assisted ventilation.
- Pain may occur in fatigued muscles (e.g., neck muscles).
- Clinical manifestations reproducible w/exercise. Observation of the pt performing repetitive muscle contractions of involved muscles will demonstrate rapidly developing weakness.
- PE may be nl at rest.
- Pts w/h/o ptosis will demonstrate fatigue weakness and ptosis when asked to sustain upward gaze for >3 min w/o interruption.

**Labs and Other Tests**
- Improvement of sx after use of anticholinesterase medications (edrophonium chloride [Tensilon] or pyridostigmine bromide [Mestinon])
- ↑ Level of AChR-Ab (present in 90% of pts w/generalized MG and 60% of pts w/ocular myasthenia). AChR-Ab titers generally do not correlate w/ clinical severity.
- Single-fiber electromyography: highly accurate in confirming MG in suspected pts w/nil conventional repetitive stimulation.
- Evaluate for presence of associated diseases.
  - MRI or CT of anterior mediastinum: thymoma found in 12%
  - TSH: thyroid disease found in 5%-15% of pts
  - Vitamin B₁₂ level: r/o pernicious anemia
  - ANA, RF (↑ association w/SLE, RA)
### Treatment
- Acetylcholinesterase inhibitors: pyridostigmine 30-60 mg PO q4-6h initially; onset of effects is 30 min, duration 4 hr
- Immunosuppressants: corticosteroids, azathioprine, mycophenolate mofetil, cyclosporine for chronic disease-modifying Rx
- Prednisone initiated at 15-20 mg qd; titrate by 5-mg increments to effect or dose of 1 mg/kg per day w/improvement in 2-4 wk and maximal response by 3-6 mo
- Azathioprine initiated at 50 mg qd, titrated to 2-3 mg/kg/day, w/clinical effect in 6-12 mo
- Mycophenolate mofetil initiated at 500 mg bid and titrated to 2-3 g per day; clinical effect in 2 wk–2 mo
- Cyclosporine initiated at 5 mg/kg/day w/clinical effect within 1-2 mo
- Plasmapheresis and IVIG are possible short-term options for immunotherapy.
- Mechanical ventilation: consider intubation if FVC <15 mL/kg, maximal expiratory pressure <40 cm H₂O, or negative inspiratory pressure <25 cm H₂O
- Thymectomy in thymomatous MG

### MYELODYSPLASTIC SYNDROME

#### Definition
Group of acquired clonal disorders affecting the hematopoietic stem cells and characterized by cytopenias w/hypercellular bone marrow and various morphologic abnormalities in the hematopoietic cell lines. Myelodysplastic syndrome cells show abnl (dysplastic) hematopoietic maturation. Marrow cellularity is ↑, reflecting an effective hematopoiesis, but inadequate maturation results in peripheral cytopenias.

#### Classification
- The French-American-British (FAB) classification is based on the proportion of immature blast cells in the blood and marrow and on the presence or absence of ringed sideroblasts or peripheral monocytosis. It includes the following: refractory anemia, refractory anemia w/ringed sideroblasts, refractory anemia w/excess blasts, chronic myelomonocytic leukemia, and refractory anemia w/excess blasts in transformation.
- The WHO classification includes the following disease subtypes: refractory anemia, refractory anemia w/ringed sideroblasts, refractory cytopenia w/multilineage dysplasia, refractory cytopenia w/multilineage dysplasia and ringed sideroblasts, refractory anemia w/excessive blasts (1, 2), unclassified myelodysplastic syndrome, and myelodysplastic syndrome associated w/isolated del(5q).

#### Diagnosis
**H&P**
- Splenomegaly, skin pallor, mucosal bleeding, ecchymosis may be present.
- Fatigue, fever, dyspnea

**Labs**
- CBC w/diff, CMP, bone marrow exam, cytogenetic analysis

#### Treatment
- Allogeneic stem cell transplantation should be considered in pts <60 yr
- Lenalidomide
- Combination chemotherapy (e.g., cytarabine + doxorubicin) induces complete response in only a minority of pts; average duration of response is <1 yr.
- Azacitidine
- Decitabine

#### Clinical Pearls
- Risk of transformation to AML varies w/% of blasts in bone marrow.
- Advanced age, male sex, and deletion of chromosomes 5 and 7 are associated w/poor prognosis.
- The most important variables in disease outcome are the specific cytogenetic abnormalities, the % of blasts in bone marrow, and the number of hematopoietic lineages involved in the cytopenias.
### MYELOID METAPLASIA WITH MYELOFIBROSIS
(MMM; AGNOCYTIC MYELOID METAPLASIA WITH MYELOFIBROSIS, IDIOPATHIC MYELOFIBROSIS)

#### Diagnosis

**H&P**
- The prominent clinical feature in MMM is marked splenomegaly due to extramedullary hematopoiesis. Palpable spleen in 80% of pts at dx.
- Some pts may experience splenic infarcts w/severe pain that may be referred to the left shoulder.
- Other common sx: peripheral edema, bone pain, arthralgias, early satiety, fatigue, anorexia and weight loss.

**Labs**
- 50% of pts present w/Hgb <10 g/dL
- Peripheral smear: myelophthisis (presence on peripheral smear of nucleated RBCs, left shifted granulocytes [metamyelocytes, myelocytes, promyelocytes, myeloblasts], and teardrop-shaped erythrocytes [dacrocytes])
- Bone marrow: fibrosis, atypical megakaryocyte hyperplasia, angiogenesis often resulting in a difficult aspiration (dry tap)
- Immunohistochemistry and cytogenetic studies

#### Treatment
- Hydroxyurea for symptomatic splenomegaly
- Splenectomy in refractory cases

#### Clinical Pearls
- MMM may present either de novo or in the setting of either PV or essential thrombocythemia.
- Incidence of transformation into acute leukemia in MMM ranges from 8%-23% in the first decade of disease.

### MYOCARDITIS

#### Definition
Inflammatory disorder of the myocardium.

#### Diagnosis

**H&P**
- Persistent tachycardia out of proportion to fever
- Faint S₁, S₄ sound on auscultation
- Murmur of MR
- Pericardial friction rub if associated w/pericarditis
- Signs of biventricular failure (hypotension, hepatomegaly, peripheral edema, distention of neck veins, S₃)
- H/o recent influenza-like syndrome (fever, arthralgias, malaise), dyspnea (72%), chest pain (32%), arrhythmias (18%)

**Labs**
- ↑ Cardiac troponin T (TnT)
- ↑ CK (w/↑ MB fraction), LDH, and AST
- ↑ ESR (nonspecific but may be of value in following the progress of the disease and the response to Rx)
- ↑ WBC (↑ eosinophils if parasitic infection)
- Viral titers (acute and convalescent)
- Cold agglutinin titer, ASO titer, blood cultures
- Lyme titer

#### Imaging
- CXR: enlargement of cardiac silhouette
- Echo: dilated and hypokinetic chambers, segmental wall motion abnormalities
- Cardiac MRI
- ECG: sinus tachycardia w/nonspecific ST-T wave changes; interventricular conduction defects and BBB
MYXEDEMA COMA

Definition
Life-threatening complication of hypothyroidism.

Diagnosis

H&P
- Profound lethargy or coma
- Hypothermia (rectal temperature <35°C [95°F]); often missed by using ordinary thermometers graduated only to 34.5°C
- Bradycardia, hypotension (secondary to circulatory collapse)
- Delayed relaxation phase of DTR, areflexia
- Myxedema facies
- Alopecia, macroglossia, ptosis, periorbital edema, nonpitting edema, doughy skin
- Bladder dystonia and distention

Labs
- Markedly ↑ TSH (if primary hypothyroidism), ↓ serum free T₄
- CBC w/diff, urine and blood cultures
- Electrolytes, BUN, Cr, LFTs, Ca, glucose
- ABGs: r/o hypoxemia and CO₂ retention

Treatment

Rx underlying cause
- CHF: diuretics, ACEIs, and salt restriction
- Ventricular arrhythmias: procainamide or quinidine
- Anticoagulation to prevent thromboembolism
- Corticosteroids justified in only selected pts w/intractable CHF, severe systemic toxicity, and severe life-threatening arrhythmias
- Immunosuppressive drugs (prednisone w/cyclosporine or azathioprine) in myocarditis from systemic autoimmune disease (e.g., SLE, scleroderma) and in pts w/i idiopathic giant cell myocarditis

Clinical Pearls
- Nearly 50% of pts w/myocarditis will die within 5 yr of dx. Prognosis is best for pts w/“fulminant” lymphocytic myocarditis (severe hemodynamic compromise, rapid onset of sx, or high fever). These pts tend to have complete recovery w/total resolution of myocarditis.
- In HIV + pts, myocarditis is the most common cardiac pathologic finding (>50%) at autopsy.
- Serum cortisol: r/o adrenal insufficiency
- ↑ CPK
- Hyperlipidemia

**Etiology**
Decompensation of hypothyroidism secondary to
- Sepsis
- Exposure to cold weather
- CNS depressants (sedatives, narcotics, antidepressants)
- Trauma, surgery

**Treatment**
- Levothyroxine 5 to 8 µg/kg (300-500 µg) IV infused over 15 min, then 100 µg IV q24h.
- Glucocorticoids should also be administered until coexistent adrenal insufficiency can be r/o. Hydrocortisone hemisuccinate 100 mg IV bolus, followed by 50 mg IV q12h or 25 mg IV q6h until initial plasma cortisol level is confirmed nl.
- IV hydration w/D5NS

### NEAR-DROWNING

#### Diagnosis
**H&P**
- Salt-water: hypertonicity, hypovolemia, hemocoagulation
- Fresh-water: hypotonicity, hypervolemia, intravascular hemolysis
- Hypoxia, hypothermia, cardiac arrhythmias, ARDS, rhabdomyolysis

**Labs**
- Metabolic acidosis, renal failure, DIC

#### Treatment
- Intubation and mechanical ventilation
- Fluid resuscitation, correction of electrolyte abnormalities
- Rx of complications (DIC, hypothermia, rhabdomyolysis, aspiration pneumonia)

### NECROTIZING FASCIITIS

#### Definition
Deep-seated infection of SC tissue that results in the progressive destruction of fascia and fat.

#### Diagnosis
**H&P**
- Diffuse swelling of an arm or leg, followed by the appearance of bullae filled w/clear fluid (can appear maroon or violaceous)
- Systemic sx may include shock and organ failure.

**Labs**
- Incision and probing of site, Gram stain, C&S

**Imaging**
- CT or MRI of affected extremity

#### Etiology
- Post surgery
- Trauma
- Causative organisms: streptococci, clostridia, mixed flora (polymicrobial: aerobic + anaerobic (*Meleney’s synergistic gangrene* if *S. aureus* + anaerobic strep), community-acquired MRSA

#### Treatment
- Surgical debridement in addition to abx
- If strep or clostridia: PCN G 24 million units/day div q4-6h IV + clindamycin 900 mg IV q8h
- If polymicrobial: imipenem or meropenem
- Add vancomycin or daptomycin if MRSA suspected
**277 NEPHROTIC SYNDROME**

**Definition**
Syndrome characterized by high urine protein excretion (>3.5 g/1.73 m²/24 hr), peripheral edema, and metabolic abnormalities (hypoalbuminemia, hypercholesterolemia).

**Diagnosis**

**H&P**
- Peripheral edema
- Ascites, anasarca
- HTN
- Pleural effusion
- Typically pts present w/severe peripheral edema, exertional dyspnea, and abd fullness secondary to ascites. There is a significant amount of weight gain in most pts.

**Labs**
- U/A: proteinuria, oval fat bodies (tubular epithelial cells w/cholesterol esters). Presence of hematuria, cellular casts, and pyuria is suggestive of nephritic syndrome.
- 24-hr urine protein excretion >3.5 g/1.73 m²/24 hr
- Blood chemistries: ↓ alb <3 g/dL, ↓ total protein, ↑ serum cholesterol, glucose, ↑ BUN, Cr
- Additional labs, depending on H&P: ANA, serum and urine immunoelectrophoresis, C3, C4, CH50, LDH, liver enzymes, alk phos, hep B and C serology, HIV

**Imaging**
- CT scan or U/S of kidneys
- CXR

**Etiology** *(Table 3-33)*
- Idiopathic (may be secondary to the following glomerular diseases: minimal-change disease [nil disease, lipoid nephrosis], focal segmental glomerular sclerosis, membranous nephropathy, membranoproliferative glomerular nephropathy)
- Systemic diseases: DM, SLE, amyloidosis, dysproteinemias
- Majority of children w/nephrotic syndrome have minimal-change disease (this form also associated w/allergy, NSAIDs, and Hodgkin’s disease).
- Focal glomerular disease: associated w/HIV, heroin abuse. A more severe form of nephrotic syndrome associated w/rapid progression to ESRD within months can also occur in HIV + pts and is known as collapsing glomerulopathy.
- Membranous nephropathy: can occur w/Hodgkin’s lymphoma, carcinomas, SLE, gold Rx
- Membranoproliferative glomerulonephropathy: often associated w/URLIs.

**Treatment**
- Bed rest as tolerated, avoidance of nephrotoxic drugs, low-fat diet, fluid restriction in hyponatremic pts; nl protein intake unless urinary protein loss >10 g/24 hr (some pts may require additional dietary protein to prevent negative nitrogen balance and significant protein malnutrition). Improved urinary protein excretion and serum lipid changes have been observed w/low-fat protein diet providing 0.7 g of protein/kg/day. However, because of ↑ risk of malnutrition, many nephrologists recommend nl protein intake.
- Sodium restriction for peripheral edema
- Monitor for development of peripheral venous thrombosis and renal vein thrombosis (↑ risk due to loss of antithrombin III and other proteins involved in the clotting mechanism).
- Furosemide for severe edema
- ACEIs to ↓ proteinuria
- Anticoagulants as long as nephrotic proteinuria or alb level <20 g/L is present
- Minimal-change disease: prednisone 1 mg/kg/day; cyclophosphamide and chlorambucil for relapses
<table>
<thead>
<tr>
<th></th>
<th>Minimal-Change Nephropathy Syndrome</th>
<th>Focal Segmental Sclerosis</th>
<th>Membranous Nephrotic</th>
<th>Membranoproliferative GN Type I</th>
<th>Membranoproliferative GN Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>75%</td>
<td>10%</td>
<td>&lt;5%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Adults</td>
<td>15%</td>
<td>15%</td>
<td>50%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Clinical manifestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>2-6</td>
<td>2-10</td>
<td>40-50</td>
<td>5-15</td>
<td>5-15</td>
</tr>
<tr>
<td>Sex</td>
<td>2:1</td>
<td>1.3:1</td>
<td>2:1 male</td>
<td>Male-female</td>
<td>Male-female</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>100%</td>
<td>90%</td>
<td>80%</td>
<td>60%</td>
<td>60%</td>
</tr>
<tr>
<td>Asymptomatic proteinuria</td>
<td>0</td>
<td>10%</td>
<td>20%</td>
<td>40%</td>
<td>40%</td>
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<tr>
<td>Hematuria</td>
<td>10%-20%</td>
<td>60%-80%</td>
<td>60%</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>HTN</td>
<td>10%</td>
<td>20% early</td>
<td>Infrequent</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Rate of progression to renal failure</td>
<td>Does not progress</td>
<td>10 yr</td>
<td>50% in 10-20 yr</td>
<td>10-20 yr</td>
<td>5-15 yr</td>
</tr>
<tr>
<td>Associated conditions</td>
<td>Allergy? Hodgkin’s disease, usually none</td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory findings</td>
<td>Manifestations of nephrotic syndrome</td>
<td>Manifestations of nephrotic syndrome</td>
<td>Renal vein thrombosis, cancer, SLE, hepatitis B,</td>
<td>None</td>
<td>Partial lipodystrophy N1 C1, C4, C3-C9</td>
</tr>
<tr>
<td></td>
<td>↑ BUN in 15%-30%</td>
<td>↑ BUN in 20%-40%</td>
<td>Manifestations of nephrotic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenetics</td>
<td>HLA-B8, B12 (3.5)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Not established</td>
<td>HLA-DRW3 (12-32)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>Not established</td>
<td>C3 nephritic factor Not established</td>
</tr>
<tr>
<td>Renal pathology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light microscopy</td>
<td>NI</td>
<td>Focal</td>
<td>Thickened</td>
<td>Thickened</td>
<td>Lobulations</td>
</tr>
<tr>
<td>Immunofluorescence</td>
<td>Negative</td>
<td>IgM</td>
<td>Fine</td>
<td>Granular</td>
<td>C3 only</td>
</tr>
<tr>
<td>Electron microscopy</td>
<td>Foot process fusion</td>
<td>Foot</td>
<td>Subepithelial</td>
<td>Mesangial</td>
<td>Dense deposits</td>
</tr>
<tr>
<td>Response of steroids</td>
<td>90%</td>
<td>15%-20%</td>
<td>May slow progression</td>
<td>Not established</td>
<td>Not established</td>
</tr>
</tbody>
</table>

<sup>*</sup>Approximate frequency as a cause of idiopathic nephrotic syndrome. About 10% of adult nephrotic syndrome is due to various diseases that usually present with AGN.

<sup>†</sup>Relative risk.

C, complement.
Chapter 3 Diseases and Disorders

- Focal and segmental glomerulosclerosis: corticosteroids; response rate 35%-40%, most pts progress to ESRD within 3 yr.
- Membranous GN: prednisone 2 mg/kg/day. Cytotoxic agents are added if there is poor response to prednisone.
- Membranoproliferative GN: corticosteroids and antiplatelet drugs

### 278 NEUROLEPTIC MALIGNANT SYNDROME (NMS)

#### Definition
Disorder characterized by hyperthermia, muscle rigidity, autonomic dysfunction, and depressed/fluctuating levels of arousal that evolve during 24-72 hr.

#### Diagnosis
**H&P**
- Muscle rigidity (hypertonia, cogwheeling, or “lead pipe” rigidity)
- Hyperthermia (38.6°C-42.3°C, usually <40°C)
- Autonomic sx: diaphoresis, sialorrhea, skin pallor, urinary incontinence
- Tachycardia, tachypnea
- Labile BP (HTN or postural hypotension)
- ΔMS (agitation, catatonia, fluctuating consciousness, obtundation)

**Labs**
- ↑ CPK (>71% of pts, w/mean value of 3700 U/L)
- Urinary myoglobin
- Leukocytosis, usually 10,000-40,000/mm³
- Electrolytes and renal function
- ABGs
- Drug levels

#### Etiology
- Unknown. Impaired thermoregulation in hypothalamus and limbic cortex may occur as a result of relative lack of dopamine activity (central dopamine-blockade hypothesis: most accepted).
- Neuroleptic drugs have different potencies for inducing NMS:
  - Typical neuroleptics: high potency, haloperidol; medium potency, chlorpromazine, fluphenazine; low potency, levomepromazine, loxapine
  - Atypical neuroleptics: low potency, risperidone, olanzapine, clozapine, quetiapine

#### Treatment
- Stop all neuroleptic agents and reinstitute any recently discontinued dopaminergic agents.
- Active cooling (cooling blanket and antipyretics)
- IV benzos (e.g., diazepam 2-10 mg, w/total daily dose of 10-60 mg) to relax muscles and to control agitation
- Bromocriptine 2.5-10 mg IV q8h and ↑ by 5 mg/day until clinical improvement is seen. The drug should be continued for at least 10 days after the syndrome has been controlled and then tapered slowly.
- Amantadine 100-200 mg PO bid
- Dantrolene 0.25 mg/kg IV q6-12h, followed by a maintenance dose up to 3 mg/kg/day. After 2-3 days, pts may be given the drug PO (25-600 mg/day in divided doses). Oral dantrolene Rx (50-600 mg/day) may be continued for several days afterward.
- Electroconvulsive Rx w/neuromuscular blockade in pharmacologically refractory cases. Succinylcholine should not be used as it may cause hyperkalemia and cardiac arrhythmias in pts w/rhabdo or dysautonomia.

### 279 NONALCOHOLIC FATTY LIVER DISEASE

#### Definition
Liver disease occurring in pts who do not abuse alcohol and manifested histologically by mononuclear cells or polymorphonuclear cells, hepatocyte ballooning, and spotty necrosis.

#### Diagnosis
Dx usually suspected on the basis of hepatomegaly, asymptomatic ↑ of transaminases, or “fatty liver” on U/S of abd
**Labs**
- ↑ ALT, AST: AST/ALT ratio is usually <1 but can ↑ as fibrosis advances.
- Negative serology for infectious hepatitis: generally nl GGTP and serum alk phos
- Hyperlipidemia (primarily hypertriglyceridemia)
- ↑ PT, hypoalbuminuria, and ↑ bili in advanced stages
- ↑ Serum ferritin, ↑ transferrin saturation in up to 10% of pts, but iron index and hepatic iron level are nl.
- Liver bx: may show a wide spectrum of liver damage ranging from simple steatosis to advanced fibrosis and cirrhosis.

**Imaging**
- U/S: diffuse ↑ in echogenicity
- CT: diffuse low-density hepatic parenchyma
- Occasionally pts may have focal rather than diffuse steatosis, which may be misinterpreted as a liver mass on U/S or CT; use of MRI in these cases will identify focal fatty infiltration.

**Etiology**
- Insulin resistance is the most reproducible factor in the development of nonalcoholic fatty liver disease.
- Risk factors are obesity (especially truncal obesity), DM, hyperlipidemia.

**Treatment**
- Weight reduction in all obese pts (500 g/wk in children and 1600 g/wk in adults)
- Medications: fenofibrates for ↑ TGs, metformin or pioglitazone for hyperglycemia

**Clinical Pearl**
- The presence of steatohepatitis or advanced fibrosis on liver bx is associated w/worse prognosis.

**280 NON-HODGKIN’S LYMPHOMA (NHL)**

**Definition**
Heterogeneous group of malignant neoplasms of the lymphoreticular system.

**Diagnosis**

**H&P**
- Asymptomatic lymphadenopathy
- Pruritus, fever, night sweats, weight loss less common than in Hodgkin’s disease
- Hepatomegaly and splenomegaly
- ½ of NHL originates extranodally. Involvement of extranodal sites can result in unusual presentations (e.g., GI tract involvement can simulate PUD).
- NHL cases associated w/HIV infection occur predominantly in the brain.

**Labs**
- Labs: CBC, ESR, U/A, LDH, BUN, Cr, serum Ca, uric acid, LFTs, serum protein electrophoresis
- β2-Microglobulin levels should be obtained initially (prognostic value) and serially in pts w/low-grade lymphomas (useful to monitor therapeutic response of the tumor).
- Bone marrow (aspirate and full bone core bx)

**Imaging**
- CXR (PA and lateral)
- CT scan of abd and pelvis; CT scan of chest if CXR abnl
- PET scan
- Bone scan (particularly in pts w/histiocytic lymphoma)

**Classification**
- The working formulation of NHL for clinical use subdivides lymphomas into low grade, intermediate grade, high grade, and miscellaneous. The WHO classification is described in Table 3-34.
- Staging: the Ann Arbor classification is used to stage NHLs (see Hodgkin’s Lymphoma). Histopathology has greater therapeutic implications in NHL than in Hodgkin’s disease.
TABLE 3-34  WHO Classification of Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>B-cell Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor B-cell lymphoma</td>
</tr>
<tr>
<td>Mature B-cell lymphoma</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
</tr>
<tr>
<td>Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)</td>
</tr>
<tr>
<td>Nodal marginal zone B-cell lymphoma</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>Mediastinal (thymic) large B-cell lymphoma</td>
</tr>
<tr>
<td>Intravascular large B-cell lymphoma</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td>Burkitt’s lymphoma/lukemia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T/NK-cell Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precursor T-cell lymphoma</td>
</tr>
<tr>
<td>Mature T/NK-cell lymphoma</td>
</tr>
<tr>
<td>Adult T-cell leukemia/lymphoma</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
</tr>
<tr>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Primary cutaneous anaplastic large-cell lymphoma</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, unspecified</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma</td>
</tr>
</tbody>
</table>

NK, natural killer; WHO, World Health Organization.

Treatment

Low-Grade NHL (e.g., nodular, poorly differentiated)
- Local RT for symptomatic obstructive adenopathy
- Deferment of Rx and careful observation in asymptomatic pts
- Single-agent chemo w/cyclophosphamide or chlorambucil and glucocorticoids
- Combination chemo alone or w/RT: when the lymphoma becomes more invasive, w/poor response to less aggressive treatment
- Monoclonal Abs: rituximab, ibritumomab
- Purine analogues (FLAMP, 2CDA): can be used in salvage treatment of refractory lymphomas

Intermediate- and High-Grade Lymphomas (e.g., diffuse histiocytic lymphoma)
- Combination chemotherapy regimens (e.g., CHOP, ProMACE-CytaBOM, MACOP-B, M-BACOD)
- Monoclonal Abs. Addition of rituximab to CHOP regimen ↑ the complete response rate and prolongs event-free and overall survival in elderly pts w/diffuse large B-cell lymphoma. Bexxar, a combination of the mononuclear Ab tositumomab and radiolabeled iodine I 131 tositumomab, can be used for a single treatment of relapsed follicular NHL in pts who are refractory to rituximab.
- Radioimmunotherapy w/131I anti-B1 Ab Rx for NHL either by itself or in combination w/other treatments
- Autologous bone marrow transplantation

Clinical Pearls
- Pts w/low-grade lymphoma, despite their long-term survival (6- to 10-yr average), are rarely cured, and the great majority (if not all) eventually die of the lymphoma, whereas pts w/high-grade lymphoma may achieve a cure w/aggressive chemotherapy.
Complete remission occurs in 35%-50% of pts w/intermediate- and high-grade lymphoma. Prognostic factors include the histologic subtype, age of pt, and bulk of disease.

Pts who present w/AIDS-related NHL and a low CD4 cell count have a poor prognosis (median duration of survival is 15-34 mo).

**281 NOSOCOMIAL INFECTIONS**

**Definition**
Infections acquired as a result of admission to health care facility, generally after 48-72 hr of admission.

**Diagnosis**

**Most Common Nosocomial Infections**
- UTIs (40%-45%)
- Surgical wound and other soft tissue infections (25%-30%)
- Pneumonia (15%-20%)
- Bacteremia (5%-12%)

**Nosocomial UTIs**
- General associations:
  - Foley catheters
  - Inappropriate catheter care (including opening catheter junctions)
  - Female sex
  - Absence of systemic abx
- Physical findings:
  - Fever
  - Dysuria
  - Leukocytosis
  - Pyuria
  - Flank or costovertebral angle tenderness
- Usual organisms:
  - *E. coli*
  - *Klebsiella*
  - *Enterobacter*
  - *Pseudomonas*
  - *Enterococcus*
- Sepsis in 1%-3% of nosocomial UTIs
- Prevention:
  - Use meticulous technique during insertion and daily perineal care.
  - Never open the catheter-collection tubing junction.
  - Obtain all specimens with sterile syringe.
  - Substitute intermittent catheterization for Foley catheters.

**Nosocomial Bacteremias**
- General associations:
  - IV lines
  - Arterial lines
  - CVP lines
  - Phlebitis
  - Hyperalimentation
- Fever possibly only presenting sign
- Exit site of all vascular lines carefully evaluated for
  - Erythema
  - Induration
  - Tenderness
  - Purulent drainage
- Usual organism for device-associated bacteremia:
  - *S. aureus* (including MRSA)
  - *Staphylococcus epidermidis* for long-term IV lines
  - *Enterobacter*
  - *Klebsiella*
  - *Candida* spp
  - *Pseudomonas aeruginosa* may come from a water source or reflect cutaneous bacteria.
Diseases and Disorders

Chapter 3

**NOSOCOMIAL INFECTIONS**

**Phlebitis** in 1.3 million pts yearly

Approximately 10,000 annual deaths from IV sepsis

Prevention:

- Meticulous sterile technique during IV insertion
- Emphasis should be placed on attention to detail, including hand washing, adherence to guidelines for catheter insertion and maintenance, appropriate use of antiseptic solutions such as chlorhexidine and iodine to prepare the skin around the catheter insertion site, and use of sterile technique for central catheter insertion.
- Modified catheter may ↓ risk for endoluminal colonization and catheter-related sepsis in subclavian lines.
- ↓ Use of routine IVs (pts would rather drink)

**Nosocomial Pneumonias**

More common in ICUs

General associations:

- Aspiration
- Intubation
- Altered consciousness
- Old age
- Chronic lung disease
- Post surgery
- Antacids

Signs of pneumonia common among pts on general wards:

- Cough
- Sputum
- Fever
- Leukocytosis
- New infiltrate on CXR
- Signs more subtle in ICUs; many pts have purulent sputum because of chronic intubation
- Change in sputum character or volume
- Small changes on CXR

Usual organisms:

- *Klebsiella*
- *Acinetobacter*
- *Enterobacter*
- *Pseudomonas aeruginosa*
- *S. aureus* (including MRSA)

Less common organisms:

- *Stenotrophomonas* spp
- *Legionella, Flavobacterium*
- Respiratory syncytial virus (infants)
- Adenovirus

1% of hospitalized pts affected

Mortality rate high (40%)

Prevention:

- Meticulous sterile technique during suctioning and handling of airway
- Do not routinely change ventilator breathing circuits and components more frequently than q48h.
- Drain respirator tubing w/o allowing fluid to return to respirator.
- Wash hands routinely to prevent colonization of pts and transfer of organisms among pts.

**Nosocomial Soft Tissue Infections**

Associations:

- Decubitus ulcers
- Surgical wound classification (contaminated or dirty-infected)
- Abd surgery
- Presence of drain
- Preoperative length of stay
- Duration of surgery >2 hr
- Surgeon
- Presence of other infection
Chapter 3  Diseases and Disorders

NOSOCOMIAL INFECTIONS

Physical findings:
- Decubitus ulcer w/fluctuance at margin or under firm eschar
- Erythema extending >2 cm beyond margin of surgical wound
- Tenderness
- Induration
- Erythema
- Fluctuance
- Purulent drainage
- Dehiscence of sutures

Usual organisms:
- S. aureus (including MRSA)
- Enterococcus
- Enterobacter
- Acinetobacter
- E. coli

Prevention:
- Careful skin care and frequent, proper positioning of pt to prevent decubitus ulcer
- Meticulous sterile surgical technique
- Hand washing to ↓ colonization when handling postoperative wound
- Limit prophylactic abx to 24 hr perioperatively.
- Double-wrap contaminated dressings (hold in gloved hand and evert gloves over dressings) before disposal.
- Rapid screening and decolonizing of nasal carriers of S. aureus w/admission and pre-op cleansing of pt’s skin with chlorhexidine.

Labs
- Cultures generally indicated for proper confirmation of responsible pathogens
  - Urine
  - Blood
  - Sputum
  - Soft tissue infection

Molecular analysis of nosocomial epidemics
- Plasmid fingerprinting
- Restriction endonuclease digestion (plasmid and genomic DNA)
- Peptide analysis by SDS-PAGE
- Immunoblotting
- Ribosomal (rRNA) typing
- DNA probes
- Multilocus enzyme electrophoresis
- Restriction fragment length polymorphism (RFLP)
- PCR
- Provide confirmation of point-source or common strains and corroboration of hypotheses reached by classic epidemiology.

Etiology

Sources and Modes of Transmission
- Pt’s own flora
  - Resistant organisms acquired during hospitalization
  - Frequently maintained thereafter by persistent GI colonization
- Unwashed hands of staff
  - Physicians
  - Nurses
- Invasion of protective defenses (intact skin, respiratory cilia, urinary sphincters, and mucosa)
  - IV lines
  - Catheters
  - Respiratory equipment
  - Surgical wounds
  - Scopes and other imaging devices
- Failure to provide adequate negative-pressure, high-volume airflow chambers for respiratory isolation of pts w/TB
Failure to rapidly identify and to provide appropriate care (w/isolation or precautions) for pts w/communicable diseases

Inanimate environment

Food

Fomites

**Risks Amplified**

- Use of broad-spectrum abx
  - Select highly resistant bacteria
  - Establish highly resistant bacteria as endemic flora in microenvironments within the hospital
- Highly vulnerable pts w/specific risk factors
  - Immunosuppression (as a result of Rx, transplantation, AIDS)
  - Old age
  - Post surgery
  - Prolonged surgery
  - Chronic lung disease
  - Ventilator dependence
  - Antacid Rx
  - Vascular lines
  - Hyperalimentation
  - ICU stay
  - Recent abx Rx
- Clustering of seriously ill pts
- Often w/wounds or drainage of contaminated materials
- Intensifying probability of cross-infection

**Handwashing Between All Pt Contacts**

- Single most important method of ↓ nosocomial infections

**Vancomycin-Resistant Enterococcus faecium (VREF)**

- VREF and other vancomycin-resistant species of enterococci account for 15%-40% of all enterococci isolated in the hospital setting.
- 80% are also ampicillin resistant.
- Factors predisposing to VREF colonization or infection include percentage of hospital days receiving antimicrobial Rx, use of IV, underlying disease, immunosuppression, and abd surgery.
- Evidence suggests that vehicle is the hands of medical personnel.

**Clostridium difficile**

- Causes diarrhea as a result of pseudomembranous colitis
- May be transmitted among hospitalized pts
- Warrants stool (contact) precautions
- Alcohol-based hand gels may not eliminate spores of this organism

**Treatment**

- Specific Rx is determined after careful consideration of resident flora within the microenvironment in which the pt was hospitalized.
- Prevention of spread of communicable diseases often requires isolation or precautions.
- Classic schema (strict, respiratory isolation and contact [skin and wound] precautions) is being replaced by more streamlined Revised Guidelines (airborne, droplet, contact isolation precautions).
- Less careful response to some diseases (e.g., hemorrhagic fevers) is inadvertently induced by removal of strict isolation category.
- Universal/standard precautions and body substance isolation continue within a new standard isolation precautions guideline.
- Universal precautions used for all pts during all contacts w/blood, body fluids, or secretions
  - Gloves
  - Goggles
  - Impermeable gowns if aerosol or splash is likely
- Consider aggressive isolation to restrict spread of resistant organisms and their plasmids
  - MRSA
  - VREF
- Highly resistant gram-negative organisms, including ESBL (extended-spectrum β-lactamases) gram-negative rods
Fungi previously considered to be contaminants now risks for pts w/cancer and organ transplantation
- Candida spp
- C. guilliermondii
- C. krusei
- C. parapsilosis
- C. tropicalis
- Aspergillus spp
- Curvularia spp
- Bipolaris spp
- Exserohilum spp
- Alternaria spp
- Fusarium spp
- Scopulariopsis spp
- Pseudallescheria boydii
- Trichosporon beigelii
- Malassezia furfur
- Hansenula spp
- Microsporum canis

### 282 OPIOID OVERDOSE

#### Diagnosis

**H&P**
- Hypoventilation, sedation, ileus, hypotension, miosis, hypothermia

**Labs**
- Toxicology screen, ethanol, acetaminophen levels, ABGs, LFTs, lytes, BUN, Cr

#### Imaging
- CXR (r/o pulmonary edema)

#### Treatment
- Establish airway and ventilation.
- Naloxone 0.1-0.4 mg IV (preferred), IM, intratracheal SC q2-3min in pts w/CNS depression w/o respiratory depression. Use 0.1 increments in opioid-dependent pts and postop to avoid CV changes.
- In pts w/respiratory depression, naloxone 2 mg IV initially (preferred), IM, intratracheal SC; may repeat up to a total dose of 10-20 mg if no reversal after initial doses. Consider IV naloxone infusion after initial dose when long-acting narcotics have been ingested.
- NG lavage followed by activated charcoal and a cathartic
- Nalmefene 1 mg SC or IM single dose is alternative to naloxone. It has longer half-life than naloxone, is effective in 5-15 min.

### 283 OPTIC NEURITIS

#### Definition

Inflammation of the optic nerve.

#### Diagnosis

**H&P**
- Visual loss develops during hours or days, most often accompanied by pain and tenderness w/movement of affected eye.
- Marcus Gunn pupil (RAPD = relative afferent pupillary defect): direct and consensual responses are nl. However, on swinging of the flashlight from eye to eye, the affected eye’s pupil dilates transiently to direct light.
- ↓ Visual acuity
- Unilateral visual field abnormalities—often a central scotoma
- Color desaturation—red most affected
- NI orbit and fundus; occasionally there is disc edema acutely, uveitis, or periphlebitis
- May have movement or light-induced phosphenes (flashes of light lasting 1-2 sec) or Uhthoff’s phenomenon (see Multiple Sclerosis).
- After several months, the optic disc may atrophy and develop pallor.
ORTHOSTATIC HYPOTENSION

Definition
Presence of at least one of the following: ↓ in systolic BP ≥20 mm Hg or ↓ diastolic BP ≥10 mm Hg within 5 min of standing.

Diagnosis
H&P
■ Dizziness, lightheadedness, syncope, weakness, diaphoresis, pallor, GI upset

Labs/Other Tests
■ CBC (r/o anemia), BUN/Cr (r/o dehydration)
■ When treatable causes of orthostatic hypotension have been ruled out, consider BP and HR monitoring with tilt table test and plasma norepinephrine measurement to distinguish postganglionic from preganglionic autonomic dysfunction.

Etiology
■ The assumption of an upright posture results in a lower arterial pressure and ↓ baroreceptor activity. The consequent ↑ in sympathetic tone at the expense of parasympathetic tone causes arterial and venous constriction as well as positive inotropic and chronotropic effects, thereby limiting the fall in BP in the upright position.
■ When orthostatic hypotension is caused by central or peripheral autonomic dysfunction, this baroreceptor reflex is impaired, and thus ↓ BP cannot be counteracted by the aforementioned compensatory mechanism.

Treatment
■ Fludrocortisone 0.1 mg/day (may combine w/α₁ agonist to ↓ the dose of each)
■ Midodrine (α₁ agonist) 10 mg tid
■ Erythropoietin (if anemic)
■ Caffeine

Clinical Pearls
■ Orthostatic hypotension is dx by observing changes in BP but not by observing changes in HR.
■ Volume depletion should ↑ HR on standing, but the HR may not change on standing in pts w/autonomic dysfunction.
■ Pharmacotherapy w/mineralocorticoids may require concomitant K⁺ replenishment and monitoring for HTN.
■ Suspect orthostatic hypotension when pt has preexisting supine HTN.
■ Suspect postural tachycardia syndrome (POTS) in patient w/marked ↑ in HR but no change in BP on standing.
Osteomyelitis

Definition
Infection involving the bones and bone marrow.

Diagnosis
H&P
- Classic presentation: bone pain, fever, chills, and generalized malaise
- Tenderness over the bone and limitations of movement of the involved extremity

Labs
- Blood cultures
- WBC: peripheral leukocytosis
- ESR: nl value does not r/o osteomyelitis; an initially ↑ ESR may be useful in following the course of the disease.
- Multiple deep cultures of a draining sinus, bone curettage, and debrided bed of any involved bones should be obtained. Aspirate and culture any joint effusions.
- The definitive dx of osteomyelitis rests on the isolation of the infective organism from bone or joint fluid obtained either by surgery or by multiple percutaneous needle biopsies.

Imaging
- Initial x-rays may be nl because radiologic changes lag behind the clinical manifestations. Positive radiographic findings usually become apparent at about 4 wk.
- Initial changes: subperiosteal elevation and soft tissue swelling → followed by lytic changes 3–4 wk later
- Radionuclide scanning (⁹⁹ᵐTc scan): can detect osteomyelitis early in its course. However, neoplasms, trauma, and other inflammatory processes may also produce abnormal radionuclide scans; normal scans in documented osteomyelitis are generally caused by impaired blood supply in the infected area. 24-hr nuclear scanning w/indium-labeled leukocytes useful to dx osteomyelitis in diabetic foot ulcers.
- MRI: most accurate imaging study for osteomyelitis
- Doppler studies: in pts w/PVD to determine vascular adequacy

Etiology
- S. aureus is the most common causative agent.
- Gram-negative bacilli: Salmonella, E. coli, Pseudomonas, Klebsiella
- Salmonella: often seen w/sickle cell disease
- Pseudomonas: more frequent in IV drug addicts; puncture wounds in sneakers
- H. influenzae: generally seen in infants and children
- Coagulase-negative staphylococci or Propionibacterium: foreign body–associated infection
- Anaerobes: often involve the sacrum (associated w/infected decubitus ulcers), skull, and hands (after human bites); diabetic foot lesions
- Bartonella henselae: HIV infection
- Pasteurella multocida or Eikenella corrodens: human or animal bites
- Others: streptococci, M. tuberculosis (generally involves spine and results in compression Fxs), fungi (C. albicans, histoplasmosis)

Treatment
Choice of abx depends on the suspected likely pathogen.
- S. aureus: cefazolin IV, nafcilin IV, vancomycin IV (in pt allergic to PCN)
- MRSA: vancomycin IV, linezolid, daptomycin, or tigecycline
- Streptococcus spp: cefazolin or ceftriaxone
- P. aeruginosa: ceftazidime + AG, piperacillin + AG, or cefepime + AG
- Enterobacteriaceae: ceftriaxone or FQ
- Duration of Rx is usually 6 wk for acute osteomyelitis; chronic osteomyelitis may need a longer course of medication.
- Hyperbaric oxygen Rx in chronic osteomyelitis
- Surgical débridement of all devitalized bone and tissue
- Immobilization of affected bone (plaster, traction) if bone is unstable
286 PAGET’S DISEASE OF BONE

Definition
Nonmetabolic disease of bone characterized by repeated episodes of osteolysis and excessive attempts at repair that result in a weakened bone with mass. Monostotic (solitary) and polyostotic (numerous) lesions may occur.

Diagnosis
H&P
Sx result mainly from the effects of complications:
- Skeletal pain, especially hip and pelvis
- Bowing of long bones, sometimes leading to pathologic Fx
- ↑ Warmth of extremity (due to ↑ vascularity)
- Skull enlargement and spinal involvement, which can produce neurologic complications (vision, hearing loss, radicular pain, and cord compression)
- Thoracic kyphoscoliosis
- Secondary osteoarthritis, especially of hip
- Heart failure as a result of chest and spine deformity and blood shunting

Imaging
- Plain x-rays: radiolucency and opacity
- Bone scan reflects activity and extent of the disease.

Labs
- ↑ Serum alk phos, nl serum Ca and phosphorus levels

Treatment
- Bisphosphonates: PO or IV
- Calcitonin: when bisphosphonates are not tolerated or contraindicated
- NSAIDs for pain relief

287 PANCREATITIS, ACUTE

Definition
- Inflammatory process of the pancreas with intrapancreatic activation of enzymes that may also involve peripancreatic tissue or remote organ systems.
- Severe acute pancreatitis: presence of any of the following 4 criteria:
  - Organ failure w/one or more of the following: shock (systolic BP <90 mm Hg), pulmonary insufficiency (Pao2 <60 mm Hg), renal failure (serum Cr >2 mg/dL after rehydration), and GI bleeding (>500 mL/24 hr)
  - Local complications such as necrosis, pseudocyst, or abscess
  - At least 3 of Ranson’s criteria (Box 3-9)
  - At least 8 of the Acute Physiology and Chronic Health Evaluation II (APACHE II) criteria

Diagnosis
H&P
- Epigastric tenderness and guarding; pain usually developing suddenly, reaching peak intensity within 10-30 min, severe and lasting several hours without relief
- Hypoactive bowel sounds (secondary to ileus)
- Tachycardia, shock (secondary to ↓ intravascular volume)
- Confusion (secondary to metabolic disturbances)
- Fever
- Tachycardia, ↓ breath sounds (atelectasis, pleural effusions, ARDS)
- Jaundice (secondary to obstruction or compression of biliary tract)
- Ascites (secondary to tear in pancreatic duct, leaking pseudocyst)
- Palpable abd mass (pseudocyst, phlegmon, abscess, carcinoma)
- Evidence of hypocalcemia (Chvostek’s sign, Trousseau’s sign)
- Evidence of intra-abd bleeding (hemorrhagic pancreatitis):
  - Gray-blue discoloration around the umbilicus (Cullen’s sign)
  - Bluish discoloration involving the flanks (Grey Turner’s sign)
- Tender SC nodules (caused by SC fat necrosis)

Labs
- ↑ Serum amylase in initial 3-5 days
- ↑ Serum lipase levels
- ↑ Serum trypsin
**Box 3-9: Assessing the Severity of Acute Pancreatitis**

**Prognostic Signs in Acute Pancreatitis (Modified Ranson)**

**At admission or dx**
- Age >55 yr
- WBC >16,000/mm³
- Blood glucose >200 mg/dL
- Serum LDH >350 IU/L
- AST >250 IU/L

**During Initial 48 Hr**
- ↓ Hct >10% w/hydration or Hct ≤30%
- ↑ BUN >5 mg/dL
- Serum Ca <8 mg/dL
- Arterial PO₂ <60 mm Hg
- Fluid sequestration >5000 mL

**Interpretation:** ↑ risk of mortality w/≥3 signs

**Major Factors Adversely Influencing Survival in Acute Pancreatitis**
- Hypotension
- Need for massive fluid and colloid replacement
- Respiratory failure
- Hypocalcemia
- Chocolate brown (hemorrhagic) peritoneal fluid

**Interpretation:** If ≥3 factors are present, mortality rate can be as high as 50%

**Banks’ Clinical Criteria for Grading the Severity of Pancreatitis**
- Cardiac: shock, tachycardia >130 bpm
- Pulmonary: arterial PO₂ <60 mm Hg; ARDS
- Renal: azotemia, urine output <50 mL/hr w/hydration
- Metabolic: ↓ serum alb, ↓ serum Ca
- Hematologic: ↓ Hct >10% w/hydration
- Neurologic: confusion, obtundation
- Abdominal: hemorrhagic peritoneal fluid, tense ascites

**Interpretation:** more signs indicate severe disease

- Rapid measurement of urinary trypsinogen-2 (if available) is useful as a screening test in pts w/abd pain; a negative dipstick test result rules out acute pancreatitis w/high degree of probability, whereas + test result indicates need for further evaluation.
- CBC: leukocytosis; Hct ↑ secondary to hemoconcentration; ↓ Hct may indicate hemorrhage or hemolysis
- ↑ BUN secondary to dehydration
- ↑ Serum glucose in previously nl pt correlates w/degree of pancreatic malfunction.
- ↑ AST and LDH due to tissue necrosis; ↑ bili and alk phos due to CBD obstruction. A ≥3× ↑ in ALT concentration is indicative of biliary pancreatitis (95% probability).
- ↓ Serum Ca due to saponification, precipitation, and ↓ PTH response
- ABGs: Pao₂ may be ↓ secondary to ARDS, pleural effusions; pH may be ↓ secondary to lactic acidosis, respiratory acidosis, and renal insufficiency.
- Serum electrolytes: potassium may be ↑ secondary to acidosis or renal insufficiency; sodium may be ↑ secondary to dehydration.

**Imaging**
- Abd plain film: useful initially to distinguish other conditions that may mimic pancreatitis (perforated viscus). It may reveal localized ileus (sentinel loop), pancreatic calcifications (chronic pancreatitis), blurring of left psoas shadow, dilation of transverse colon, calcified gallstones.
- CXR: may reveal elevation of one or both diaphragms, pleural effusions, basilar infiltrates, plate-like atelectasis.
- Abd U/S: useful in detecting gallstones (sensitivity 60%-70%), pancreatic pseudocysts; its major limitation is the presence of distended bowel loops overlying the pancreas.
CT abd: superior to U/S in identifying pancreatitis and defining its extent, and it also plays a role in diagnosis of pseudocysts (they appear as a well-defined area surrounded by a high-density capsule); GI fistulation or infection of a pseudocyst can also be identified by the presence of gas within the pseudocyst. Sequential contrast-enhanced CT is useful for detection of pancreatic necrosis. The severity of pancreatitis can also be graded by CT scan. (A = nl pancreas, B = enlarged pancreas [1 point], C = pancreatic or peripancreatic inflammation [2 points], D = single peripancreatic collection [3 points], E = at least 2 peripancreatic collections or retroperitoneal air [4 points]. % of pancreatic necrosis <30% [2 points], 30%-50% [4 points], >50% [6 points]. The CT severity index is calculated by adding grade points to points assigned for percentage of necrosis.)

MRCP: useful if a surgical procedure is not anticipated

ERCP: should not be performed during the acute stage of disease unless it is necessary to remove an impacted stone in the ampulla of Vater

**Etiology**

- >90% of cases: biliary tract disease (calculi or sludge) or alcohol
- Drugs: thiazides, furosemide, corticosteroids, tetracycline, estrogens, valproic acid, metronidazole, azathioprine, methylodpa, pentamidine, ethacrynic acid, procainamide, sulindac, nitrofurantoin, ACEIs, danazol, cimetidine, piroxicam, gold, ranitidine, sulfasalazine, isoniazid, aceterminophen, cisplatin, opiates, erythromycin
- Abd trauma
- Surgery
- ERCP
- Infections (predominantly viral infections)
- PUD
- Pancreas divisum (congenital failure to fuse of dorsal or ventral pancreas)
- Pregnancy
- Vascular (vasculitis, ischemic)
- Hypolipoproteinemia (types I, IV, and V)
- Hypercalcemia
- Pancreatic carcinoma (primary or metastatic)
- Renal failure
- Hereditary pancreatitis
- Occupational exposure to chemicals: methanol, cobalt, zinc, mercuric chloride, creosol, lead, organophosphates, chlorinated naphthalenes
- Others: scorpion bite, obstruction at ampulla region (neoplasm, duodenal diverticula, Crohn’s disease), hypotensive shock, autoimmune pancreatitis

**Treatment**

**General Measures**

- Maintain adequate intravascular volume w/vigorous IV hydration.
- Pt should remain NPO until clinically improved, stable, and hungry. Enteral feedings are preferred to TPN. Parenteral nutrition may be necessary in pts who do not tolerate enteral feeding or in whom an adequate infusion rate cannot be reached within 2–4 days.
- NG suction is useful in severe pancreatitis to decompress the abd in pts w/ ileus.
- Control pain: IV morphine or fentanyl.
- Correct metabolic abnormalities (e.g., replace Ca and Mg as necessary).

**Specific Measures**

- Pancreatic or peripancreatic infection develops in 40%-70% of pts w/pancreatic necrosis. However, IV abx should not be used prophylactically for all cases of pancreatitis; their use is justified if the pt has evidence of septicemia, pancreatic abscess, or pancreatitis secondary to biliary calculi. Their use should generally be limited to 5–7 days to prevent development of fungal superinfection. Appropriate empiric abx Rx should cover
  - *B. fragilis* and other anaerobes (cefotetan, cefoxitin, metronidazole, or clindamycin + AG)
  - *Enterococcus* (ampicillin)
Surgical Rx indicated in the following:
- Gallstone-induced pancreatitis: cholecystectomy when acute pancreatitis subsides
- Perforated peptic ulcer
- Excision or drainage of necrotic or infected foci. Necrosectomy (debridement) w/placement of wide-bore drains for continuous postoperative irrigation is the preferred surgical procedure.

Identification and treatment of complications:
- Pseudocyst: round or spheroid collection of fluid, tissue, pancreatic enzymes, and blood
  - Dx: CT scan or sonography
  - Rx: CT scan or U/S-guided percutaneous drainage (w/pigtail catheter left in place for continuous drainage) can be used, but the recurrence rate is high; the conservative approach is to re-evaluate the pseudocyst (w/CT scan or U/S) after 6-7 wk and surgically drain it if the pseudocyst has not ↓ in size. Pseudocysts <5 cm in diameter are generally reabsorbed w/o intervention, whereas those >5 cm require surgical intervention after the wall has matured.
- Phlegmon: represents pancreatic edema
  - Dx: CT scan or U/S
  - Rx: supportive measures; it usually resolves spontaneously.
- Pancreatic abscess
  - Dx: CT scan (presence of bubbles in the retroperitoneum); Gram staining and cultures of fluid obtained from guided percutaneous aspiration usually identify bacterial organism.
  - Rx: surgical (or catheter) drainage and IV abx (imipenem-cilastatin)
- Pancreatic ascites: usually caused by leaking of pseudocyst or tear in pancreatic duct
  - Dx: paracentesis reveals ↑↑ amylase and lipase levels in the pancreatic fluid; ERCP may demonstrate the lesion
  - Rx: surgical correction if exudative ascites from severe pancreatitis does not resolve spontaneously
- GI bleeding: caused by alcoholics gastritis, bleeding varices, stress ulceration, or DIC
- Renal failure: caused by hypovolemia resulting in oliguria or anuria, cortical or tubular necrosis (shock, DIC), or thrombosis of renal artery or vein
- Hypoxia: caused by ARDS, pleural effusion, or atelectasis

Clinical Pearls
Prognosis varies w/severity of pancreatitis; overall mortality in acute pancreatitis is 5%-10%; poor prognostic signs according to the Ranson criteria are as follows:
- Age >55 yr
- Fluid sequestration >6000 mL
- Laboratory abnormalities on admission: WBC >16,000, blood glucose >200 mL/dL, serum LDH >350 IU/L, AST >250 IU/L
- Laboratory abnormalities during the initial 48 hr: ↓ Hct >10% w/hydration or Hct <30%, BUN rise >5 mg/dL, serum Ca <8 mg/dL, arterial Po2 <60 mm Hg, and base deficit >4 mEq/L

288 PANCREATITIS, CHRONIC

Definition
Recurrent or persistent inflammatory process of the pancreas characterized by chronic pain and by pancreatic exocrine or endocrine insufficiency.

Diagnosis
H&P
- Persistent or recurrent epigastric and LUQ pain, may radiate to the back
- Tenderness over the pancreas, muscle guarding
- Significant weight loss
- Bulky, foul-smelling stools, greasy in appearance
- Epigastric mass (10% of pts)
- Jaundice (5%-10% of pts)
Diseases characterized disorder clinically by neurodegenerative rigidity, by sions. Progressive Definition

Labs
- ↑/N serum amylase and lipase
- ↑ Glucose, bili, alk phos, glycosuria
- 72-hr fecal fat determination (rarely performed) reveals excess fecal fat. Fecal elastase test requires only 20 g of stool.
- Secretin stimulation test: used for diagnosis of pancreatic exocrine insufficiency
- Lipid panel: ↑↑ TGs can cause pancreatitis
- Serum Ca: hyperparathyroidism is a rare cause of chronic pancreatitis.
- ↑ Serum IgG4 is found in sclerosing pancreatitis and autoimmune pancreatitis.
- ↑ Serum Ig or γ-globulin level, presence of antilactoferrin Ab, anti–carbonic anhydrase II level, ASMA, or ANA in autoimmune pancreatitis

Imaging
- Plain abd radiographs: may reveal pancreatic calcifications (95% specific for chronic pancreatitis)
- U/S abd: duct dilation, pseudocyst, calcification, presence of ascites
- Contrast-enhanced CT scan of abd: useful for detection of calcifications, to evaluate for ductal dilation, and to r/o pancreatic cancer
- EUS: sensitivity of 97% and a specificity of 60% for chronic pancreatitis
- FNAB combined w/EUS is the preferred modality for evaluation of cystic or mass lesions to determine malignancy.
- MRCP: preferred to ERCP

Etiology
- Chronic alcoholism
- Obstruction (ampullary stenosis, tumor, trauma, pancreas divisum, annular pancreas)
- Hereditary pancreatitis
- Severe malnutrition
- Idiopathic
- Untreated hyperparathyroidism (hypercalcemia)
- Mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene and the TF genotype
- Autoimmune (sclerosing) pancreatitis (5% of chronic pancreatitis cases): presents clinically w/jaundice (63% of pts) and abd pain (35%). CT may reveal diffusely enlarged pancreas, enhanced peripheral rim of hypoattenuation “halo,” and low-attenuation mass in head of pancreas. Labs reveal elevated serum IgG4, ↑ serum Ig or γ-globulin level, + antilactoferrin Ab, anti–carbonic anhydrase II level, ASMA, or ANA.

Treatment
- Steatorrhea Rx w/pancreatic supplements [e.g., pancrease, pancrelipase [Creon] titrated PRN on the basis of the amount of steatorrhea and pt’s weight loss]
- Glucocorticoid in autoimmune pancreatitis
- Surgical intervention in pts w/obstruction of pancreatic duct
- Transduodenal sphincteroplasty or pancreaticojejunostomy in pts w/intractable pain

Clinical Pearls
- Long-term survival is poor (50% of pts die within 10 yr of chronic pancreatitis or malignant neoplasm).
- Prognosis is best in pts w/recurrent acute pancreatitis from cholelithiasis, hyperparathyroidism, or stenosis of the sphincter of Oddi.

289 PARKINSON’S DISEASE (PD)

Definition
Progressive neurodegenerative disorder characterized clinically by rigidity, tremor, and bradykinesia and pathologically by cytoplasmic eosinophilic inclu-

sions (Lewy bodies) in neurons of the substantia nigra and locus caeruleus and by depigmentation of the brainstem nuclei.
Diagnosis
- Begins insidiously w/slight loss of motor dexterity, generalized slowness, or ↓ in overall motor activity
- Classic manifestations are
  - Rigidity: ↑ muscle tone involving both agonist and antagonist muscle groups. Resistance to passive movement is widespread and more prominent at large joints (cogwheeling rigidity is noted).
  - Tremor: resting tremor, w/frequency of 4–7 movements/sec. It often begins unilaterally and distally and spreads proximally and to the other side during months or years. Tremor is usually noted in the hands and often involves the thumb and forefinger (pill-rolling tremor).
  - Akinesia: inability to initiate or to execute a movement. The pt often sits immobile because even the simple task of getting up from a chair becomes impossible. The face shows a marked absence of movement (masked facies); the mouth is usually open, and the pt drools.
  - Gait disturbance: the pt assumes a stooped posture (head bowed, trunk bent forward, shoulders dropped; knees and arms flexed, “soccer goalie stand”). There is difficulty initiating the first step, and this is followed by small shuffling steps that ↑ in speed (festinating gait) as if the pt is chasing his/her center of gravity (the pt’s steps become progressively faster and shorter while the trunk inclines farther forward).
  - Abnl reflexes: stroking the palm of the hand near the base of the thumb results in contraction of the ipsilateral mentalis muscle, causing wrinkling of the skin of the chin (palpomental reflex). Repeated gentle tapping on the glabella evokes blinking of both eyes (glabellar reflex).
  - Postural instability: tested by pull test. Ask pt to stand in place w/back to examiner. Examiner pulls pt back by the shoulders, and proper response would be to take no steps back or very few steps back w/o falling. Retropulsion is a positive test result, as is falling straight back. This is not usually severe early on. If falls occur and postural reflexes are greatly impaired early on, then consider other disorders.
  - Dementia: occurs in approximately 25%-50% of pts
  - Others: orthostatic hypotension, micrographia, diminished blinking, inaudible speech; difficulty opening a jar, turning in bed

Treatment
- Physical therapy, pt education and reassurance, treatment of associated conditions (e.g., depression)
- Avoidance of drugs that can induce or worsen parkinsonism: neuroleptics (especially high potency), certain antiemetics (prochlorperazine, trimethobenzamide), metoclopramide, nonselective MAOls (may induce hypertensive crisis), reserpine, methylidopa
- Rx initiated when disease starts to affect pt’s quality of life
- Goal of Rx is symptomatic and not curative.
- If sx very mild, can consider MAO-B inhibitor or amantadine.
- Once decision is made to start dopaminergic Rx, either agonists or levodopa can be used as first line. Decision is based on relative impact of improving motor disability (levodopa) compared w/lessening of motor complications (dopamine agonist). In general, consider use of dopamine agonist in young pts as first-line Rx. In pts >70 yr of age, levodopa is drug of choice.

Chronic Rx
- Levodopa Rx:
  - Cornerstone of symptomatic Rx. Should be used w/peripheral dopa decarboxylase inhibitor (carbidopa) to minimize side effects (nausea, lightheadedness, postural hypotension). The combination of the two drugs is marketed under the trade name Sinemet.
  - Usual starting dose is 25/100 mg (carbidopa/levodopa) tid 1 hr before meals.
  - Stalevo (combination Sinemet and entacapone, a catechol-O-methyltransferase inhibitor): useful for pts w/motor fluctuations (wearing off)
  - Dopamine receptor agonists (ropinirole, pramipexole, bromocriptine, and rotigotine) are not as potent as levodopa, but they are often used as
initial treatment in younger pts to attempt to delay the onset of complications (dyskinesias, motor fluctuations). These medications are more expensive than levodopa. In general, they cause more side effects, such as N/V, lightheadedness, peripheral edema, confusion, and somnolence, than levodopa does. They can also cause a dopamine dysregulation syndrome, which includes compulsive behaviors such as pathologic gambling and hypersexuality. All pts taking these drugs should be asked about the presence of these sx. Nothing suggests that one agonist is better than another.

• MAO-B inhibitors (selegiline, rasagiline): can be used early as initial Rx in those w/very mild disease or as adjunctive Rx. It is still unknown whether these drugs have neuroprotective effects or only mild symptomatic benefits.

• Amantadine: can be used alone early in the disease. It is especially useful in the treatment of dyskinesias. Dosage is 100 mg tid (titrate q wk from 100 mg qd). Must adjust for elderly and renal impairment. Most notable side effect, especially in elderly, is confusion and livedo reticularis.

• Anticholinergic agents (trihexyphenidyl, benztropine) are helpful in treating the tremor and drooling in pts w/PD and can be used alone or in combination w/levodopa; potential side effects include constipation, urinary retention, memory impairment, and hallucinations. They should be avoided in the elderly. In general, role is limited to young pts w/tremor and no (or min.) other associated signs/sx of PD.

Surgical options

• Pallidal (globus pallidus interna) and subthalamic deep brain stimulation is currently the surgical option of choice; thalamic deep brain stimulation may be useful for refractory tremor.

• Surgery is limited to pts w/disabling, medically refractory problems, and pts must still have a good response to levodopa to undergo surgery. Deep brain stimulation results in ↓ dyskinesias, fluctuations, rigidity, and tremor.

290 PAROXYSMAL ATRIAL TACHYCARDIA (PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA, PSVT)

Definition

SVT includes all forms of tachycardia that either arise above the bifurcation of the bundle of His or that have mechanisms dependent on the bundle of His. AV nodal reentrant tachycardia is the most common type (60%) of SVT; 30% are due to an AV reentry circuit mediated by an accessory pathway (a short muscle bundle directly connecting the atria and ventricles), 10% are due to atrial tachycardia.

Diagnosis

ECG (Fig. 3-39):

• Absolutely regular rhythm at rate of 150-220 bpm is present.

• P waves may or may not be seen (the presence of P waves depends on the relationship of atrial to ventricular depolarization).

• Wide QRS complex (>0.12 sec) w/initial slurring (delta wave, see Fig. 3-49) during sinus rhythm and short PR (<0.12 sec) are characteristic of WPW syndrome.

Etiology

• Young pts w/o evidence of cardiac disease (and, thus, the etiology is really just a reentrant tract)

• Preexcitation syndromes (e.g., WPW syndrome)

• ASD

• Acute MI

• When evaluating pts, it is important to assess for triggers (e.g., intake of alcohol, caffeine, and other drugs) and presentation (in contrast to sinus tachycardia, which accelerates and decelerates gradually, SVTs have sudden onset and termination).
**Chapter 3  Diseases and Disorders**

**Diseases and Disorders**

**PAROXYSMAL ATRIAL TACHYCARDIA**

Treatment

- **Valsalva maneuver** in the supine position is the most effective way to terminate SVT; carotid sinus massage (after excluding occlusive carotid disease [absence of carotid bruit and no hx suggestive of carotid artery disease]) or application of an ice pack to the face in children is also commonly used to elicit vagal efferent impulses.

- **Synchronized DC shock** if pt shows signs of cardiogenic shock (is hypotensive), angina, or CHF

- **Adenosine:** for Rx of PSVT that is unresponsive to vagal maneuvers; the dose is 6 mg given as a rapid IV bolus under ECG monitoring; tachycardia is usually terminated within a few seconds in 60%-80% of pts; if necessary, the drug can be given again w/ 12 mg IV bolus (effective in terminating PSVT in >90% of pts). Contraindications are second- or third-degree AV block, SSS, AF, and VT. Adenosine is also contraindicated in heart transplant pts and should be used w/caution in COPD pts. It may also cause bronchospasm in asthmatic pts.

- If adenosine is not effective, verapamil 2.5-5 mg IV q5min to a max of 15 mg is generally effective
  - **Verapamil should be used cautiously in pts w/SVT and h/o hypotension.** If the pt is truly hypotensive w/SVT, immediate synchronized cardioversion is indicated.
  - **Slow injection of Ca chloride (10 mL of a 10% solution) given during 5-8 min before verapamil administration may ↓ the hypotensive effect w/o compromising its antiarrhythmic effect.**
  - **Repeat carotid massage after IV verapamil if SVT persists.**

- **β-Blockers** (metoprolol [5 mg IV q2min up to 15 mg] or esmolol [500 mg/kg IV bolus, then 50 mg/kg/min]) or IV diltiazem, IV procainamide, IV propafenone, IV flecainide, or IV ibutilide may also be effective in the treatment of SVT; however, these agents generally have little role in acute

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**Figure 3-39.** Supraventricular tachycardia (paroxysmal atrial tachycardia [PAT]). The upper and lower rows are part of one continuous strip. In the upper row, no definite P waves are visible. The diagnosis of this ECG is therefore supraventricular tachyarrhythmia. The ventricular rate is approximately 185/min. In the lower strip, taken at the end of the carotid sinus massage, sinus rhythm has appeared. However, the heart rate is still rapid (approximately 135/min).
management of PSVT. Digoxin should also be avoided in pts w/ WPW syndrome and narrow QRS tachycardia (risk of AF during AV reentrant tachycardia).

291 PAROXYSMAL COLD HEMOGLOBINURIA (PCH)

Definition
Rare disorder characterized by episodic massive intravascular hemolysis after exposure to cold temperatures. Hemolysis may occur in an idiopathic form in adults or, more commonly, after a viral infection in children.

Diagnosis
H&P
- After cold exposure, red to brown urination begins within minutes to hours.
- Associated sx include back, leg, and abd pain.
- Headaches, N/V, and diarrhea are common.
- May be associated w/ RP
- Associated w/ cold urticaria
- Transient splenomegaly and jaundice may occur.
- Sx and gross hemoglobinuria usually resolve within hours.
- Sx are thought to be mediated by smooth muscle dysfunction secondary to nitric oxide toxicity associated w/ hemoglobinemia.

Labs
- The presence of IgG that reacts w/ the RBC at temperatures but not at body temperature. In the Donath-Landsteiner test, a pt’s serum is incubated w/ donated RBCs and complement at 4°C, then warmed to 37°C. Lysis is observed in a + test result.
- A more sensitive test involves use of radiolabeled monoclonal anti-IgG. This is incubated at 4°C w/ the pt’s serum and donor RBCs. The degree of radioactivity on the separated RBCs will be ↑ in PCH compared w/ a control run at 37°C.
- ↑ Bili and LDH
- Abnormal RBC forms, such as poikilocytosis, spherocytosis, and anisocytosis
- Erythrophagocytosis by neutrophils and monocytes may be seen.

Etiology
- Polyclonal IgG (Donath-Landsteiner Ab) binds to P antigen on RBC membrane when blood is exposed to cold temperatures. As blood warms to body temperature, complement-mediated hemolysis ensues.
- In children, the appearance of the Ab usually follows the onset of a viral respiratory illness by 7-10 days. Sx may persist for several weeks.
- PCH has been associated w/ multiple infectious pathogens, including syphilis, H. influenzae, EBV, CMV, influenza A, varicella, measles, mumps, and adenovirus.

Treatment
- Avoidance of exposure to cold
- Transfusion if anemia life-threatening
- Steroids generally not helpful
- Splenectomy not indicated

292 PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

Definition
Rare disease characterized by episodes of intravascular hemolysis and hemoglobinuria usually occurring at night.

Diagnosis
H&P
- Initial manifestations
  - Anemia sx (35%)
  - Hemoglobinuria (25%): typically the first morning void reveals dark urine w/ progressive clearing during the day. The cause for the circadian rhythm is unknown.
  - Bleeding (20%)
• Aplastic anemia (15%)
• GI sx (10%)
• Hemolytic anemia (10%): episodes of hemolytic exacerbations can accompany infections, menstruation, transfusion, surgery, iron Rx, and vaccinations. Sx of severe hemolysis include chest, back, or abd pain and headache, fever, malaise, and fatigue.
• Infections (5%)

■ Physical findings
  • Pallor (anemia)
  • Jaundice (hemolysis)
  • Splenomegaly
  • Unilateral extremity swelling (DVT)
  • Ascites (Budd-Chiari syndrome)

Labs
■ CBC: anemia, leukopenia, thrombocytopenia
■ Reticulocytosis
■ RBC smear: spherocytes
  – Coombs’ test result
  ↓ Leukocyte alk phos
  ↑ LDH
  ↓ Serum haptoglobin
  ↓ Serum iron saturation, ↓ ferritin
  ↑ Urine Hgb
  ↑ Urine urobilinogen
  ↑ Urine hemosiderin
  + Ham test (acidified serum RBC lysis)
■ Normoblastic hyperplasia on bone marrow exam
■ Identification of glycophosphatidylinositol-anchored protein deficiency on hematopoietic cells by monoclonal Abs or flow cytometry. Flow cytometric analysis of granulocytes is the best way to dx PNH (∧ decay-accelerating factor [DAF]).

Treatment
■ Prednisone
■ Eculizumab 600 mg IV q wk × 4 wk, then 900 mg × 1 wk, then 900 mg q2wk for maintenance dose
■ Iron replacement, folic acid supplementation
■ Transfusions
■ Treatment and prevention of thrombosis (heparin, coumadin)
■ Avoidance of oral contraceptives
■ Bone marrow transplantation

293 PEDICULOSIS

Definition
Lice infestation. Humans can be infested w/3 kinds of lice: Pediculus capitis (head louse), Pediculus corporis (body louse), and Phthirus pubis (pubic, or crab, louse). Lice feed on human blood and deposit their eggs (nits) on the hair shafts (head lice and pubic lice) and along the seams of clothing (body lice). Nits generally hatch within 7-10 days. Lice are obligate human parasites and cannot survive away from their hosts for >7-10 days.

Diagnosis
■ Pruritus w/excoriation: caused by hypersensitivity reaction, inflammation from saliva, and fecal material from the lice.
■ Nits can be identified by examining hair shafts.
■ Lymphadenopathy may be present (cervical adenopathy w/head lice, inguinal lymphadenopathy w/pubic lice).
■ Head lice are most frequently found in the back of the head and neck, behind the ears.
■ Scratching can result in pustules and crusting.
■ Wood’s light examination: useful to screen a large number of children; live nits fluoresce, empty nits have a gray fluorescence, nits w/unborn louse reveal white fluorescence.
Treatment
- Permethrin: available OTC (1% permethrin) or by prescription (5% permethrin), applied to the hair and scalp and rinsed out after 10 min. Resistance to permethrin is increasing.
- Benzyl alcohol lotion 5% (ulesfia): applied to dry hair × 10 min then rinsed, repeated 7 days later; well tolerated.
- Malathion: effective in head lice. Use should be avoided in children ≤ 6 yr; expensive.
- TMP-SMX double strength bid × 10 days: effective for head lice infestation in pts who have previously failed treatment or in whom resistance w/1% permethrin cream rinse occurs.
- Ivermectin single oral dose of 200 μg/kg: effective for head lice resistant to other treatments. Contraindicated in children weighing < 15 kg

Clinical Pearls
- Pts w/body lice should discard infested clothes.
- Personal items such as combs and brushes should be soaked in hot water for 15-30 min.

294 PELVIC INFLAMMATORY DISEASE (PID)

Definition
Spectrum of inflammatory disorders of the upper genital tract among women, which may include any combination of endometritis, salpingitis, tubo-ovarian abscess, and pelvic peritonitis.

Diagnosis
- Min. criteria for dx PID:
  - Uterine/adnexal tenderness or
  - Cervical motion tenderness
- Additional criteria:
  - Oral temperature > 38.3°C (101°F)
  - Abnl cervical or vaginal mucopurulent d/c
  - Presence of WBCs on saline microscopy of vaginal secretions
  - ↑ ESR
  - ↑ C-reactive protein level; and
  - Lab documentation of cervical infection w/N. gonorrhoeae or C. trachomatis
- Other criteria:
  - Laparoscopic abnormalities consistent w/PID
  - Histopathologic evidence of endometritis on endometrial bx
  - Imaging: transvaginal U/S or CT showing thickened fluid-filled tubes w/ or w/o free pelvic fluid or tubo-ovarian complex. MRI pelvis (sensitivity 95%, specificity 89%, accuracy 93%)

Etiology
- N. gonorrhoeae and C. trachomatis are implicated in the majority of cases.
- Microorganisms that can be part of the vaginal flora, such as anaerobes, G. vaginalis, H. influenzae, enteric gram-negative rods, and S. agalactiae, can also cause PID.

Treatment
- Outpatient treatment, Regimen A: ceftriaxone 250 mg IM or IV × 1 dose + doxycycline 100 mg PO bid × 14 days w/ or w/o metronidazole 500 mg PO bid × 14 days
- Outpatient treatment, Regimen B:
  - Cefoxitin 2 g IM + probenecid 1 g PO single dose + doxycycline 100 mg PO bid × 14 days w/ or w/o metronidazole 500 mg PO bid × 14 days or
  - Ceftriaxone 250 mg IM once single dose + doxycycline 100 mg PO bid × 14 days w/metronidazole 500 mg PO bid × 14 days
- Inpatient treatment, Regimen A:
  - Cefoxitin 2 g IV q6h or cefotetan 2 g IV q12h + doxycycline 100 mg IV or PO q12h
  - Continuation of regimen for at least 24 hr after substantial clinical improvement, after which doxycycline 100 mg PO bid is continued for a total of 14 days
Inpatient treatment, Regimen B:
- Clindamycin 900 mg IV q8h + gentamicin loading dose IV or IM (2 mg/kg of BW), followed by a maintenance dose (1.5 mg/kg) q8h
- Continuation of regimen for at least 24 hr after substantial clinical improvement, followed by doxycycline 100 mg PO bid to complete a total of 14 days of Rx

Alternative parenteral regimen:
- Ampicillin-sulbactam 3 g IV q6h + doxycycline 100 mg PO or IV q12h

Clinical Pearls
- Outpatient management of PID is appropriate for most pts; however, follow-up within 72 hr is recommended to assess the pt’s response to antimicrobial Rx.
- Hospitalization is recommended when the following criteria are met:
  - Surgical emergencies such as appendicitis cannot be excluded
  - Pregnancy
  - Tubo-ovarian abscess
  - Severe illness, N/V, or high fever
  - Pt unable to follow or to tolerate an outpatient oral regimen
  - Poor clinical response to oral antimicrobial Rx

PEPTIC ULCER DISEASE (PUD)

Definition
Ulceration in the stomach or duodenum.

Diagnosis
H&P
- Exam often unremarkable
- Epigastric tenderness, tachycardia, pallor, hypotension (from acute or chronic blood loss), N/V (if pyloric channel is obstructed), boardlike abd and rebound tenderness (if perforated), and hematemesis or melena (w/a bleeding ulcer)

Labs
- CBC: anemia in pts w/significant GI bleeding
- *H. pylori* testing by endoscopic bx, urea breath test, stool antigen test (*H. pylori* stool antigen). Serum Ab test does not differentiate between current and prior infection.

Imaging
- Dx modalities include endoscopy or UGI series. Endoscopy is preferred.

Etiology
Often multifactorial; the following are common mucosal damaging factors:
- *Helicobacter pylori* infection
- Medications (NSAIDs, glucocorticoids)
- Incompetent pylorus or LES
- Bile acids
- Impaired proximal duodenal bicarbonate secretion
- ↓ Blood flow to gastric mucosa
- Acid secreted by parietal cells and pepsin secreted as pepsinogen by chief cells
- Cigarette smoking
- Alcohol

Treatment
- *H. pylori* + pts:
  - PPI + clarithromycin 500 mg bid and amoxicillin 1000 mg bid for 7-10 days
  - PPI bid + amoxicillin 500 mg bid + metronidazole 500 mg bid for 7-10 days
  - PPI bid + clarithromycin 500 mg bid and metronidazole 500 mg bid for 7 days
- *H. pylori*-pts: H2RAs (famotidine, ranitidine) or PPIs
- All pts: avoid tobacco, NSAIDs, and alcohol
Clinical Pearl
- In pts w/recurrent peptic ulcer bleeding, high-dose IV esomeprazole after successful endoscopic Rx ↓ risk of recurrent bleeding.

296 PERICARDIAL TAMПONADE

Definition
Pericardial effusion that significantly impairs diastolic filling of the heart.

Diagnosis
H&PP
- Dyspnea, orthopnea
- Interscapular pain
- Beck’s triad: distended neck veins, distant heart sounds, hypotension
- ↓ apical impulse
- Diaphoresis, tachypnea
- Tachycardia (compensatory to maintain CO)
- Ewart’s sign: an area of dullness at the angle of the left scapula, caused by compression of the lung by the pericardial effusion
- Pulsus paradoxus (↓ in systolic BP >10 mm Hg during inspiration)
- Hypotension
- Narrowed pulse pressure

Imaging
- CXR: cardiomegaly (water bottle configuration of the cardiac silhouette) w/clear lung fields; CXR may be nl when acute tamponade occurs rapidly in absence of prior pericardial effusion.
- Echo: detects effusions as small as 30 mL (they are seen as an echo-free space): paradoxical wall motion can also be seen.
  - Two-dimensional echo may reveal prolonged diastolic collapse or inversion of right atrial free wall.
  - Early diastolic collapse of right ventricular wall is also suggestive of cardiac tamponade.
  - Paradoxical movement of the septum
  - Echo may miss localized effusions laterally adjacent to right atrium.
- Cardiac catheterization
  - Equalization of pressures within chambers of the heart
  - Elevation of RAP w/a prominent x but no significant y descent.
- MRI
- ECG
  - Amplitude of the QRS complex
  - Variation of the R wave amplitude from beat to beat (electrical alternans); this results from the heart oscillating in the pericardial sac from beat to beat. More common w/neoplastic effusions.

Treatment
- Immediate pericardiocentesis under echo, fluoroscopy, or CT; send aspirated fluid for analysis (protein, LDH, cytology, cell count, Gram stain, AFB stain) and cultures for AFB, fungi, and bacterial cultures and sensitivity.
- Placement of a percutaneous drainage catheter or pericardial window draining into the pleural cavity in pts w/recurrent effusions (e.g., neoplasms)
- Colchicine: possibly useful in relapsing acute pericarditis and idiopathic chronic large pericardial effusion w/o tamponade
- Pericardiectomy: in pts w/idiopathic chronic pericardial effusion

Clinical Pearls
- Pericardial tamponade occurs in 15% of pts w/idiopathic pericarditis but in nearly 60% of those w/neoplastic, tuberculous, or purulent pericarditis.
- Effusive-constrictive pericarditis:
  - Uncommon pericardial syndrome characterized by concomitant tamponade caused by tense pericardial effusion and constriction caused by the visceral pericardium
  - It may be missed in some pts who present w/tamponade.
• Although evolution to persistent constriction is frequent, idiopathic cases may resolve spontaneously.
• Extensive epicardectomy is the procedure of choice in pts requiring surgery.

**PERICARDITIS**

**Definition**
Inflammation (or infiltration) of the pericardium.

**Diagnosis**

**H&P**
- Severe constant pain that localizes over the anterior chest and may radiate to arms and back; it can be differentiated from myocardial ischemia because the pain intensifies w/inspiration and is relieved by sitting up and leaning forward (the pain of myocardial ischemia is not pleuritic).
- Pericardial friction rub: best heard w/pt upright and leaning forward and by pressing the stethoscope firmly against the chest; it consists of 3 short, scratchy sounds:
  - Systolic component
  - Diastolic component
  - Late diastolic component (associated w/atrial contraction)
- Cardiac tamponade may be occurring if the following are observed:
  - Tachycardia
  - BP and pulse pressure
  - Distended neck veins
  - Paradoxical pulse

**Labs**
The following tests may be useful in absence of an obvious cause:
- CBC w/diff
- Viral titers (acute and convalescent)
- ESR
- ANA, RF
- PPD, ASO titers
- BUN, Cr
- Blood cultures
- Cardiac isoenzymes (usually nl, but mild elevations of CK-MB may occur because of associated epicarditis)

**Imaging**
- Echo: to detect and to determine amount of pericardial effusion; absence of effusion does not r/o dx of pericarditis. Divergence of right and left ventricular systolic pressures is present in cardiac tamponade and constrictive pericarditis.
- CXR: cardiac silhouette appears enlarged if more than 250 mL of fluid has accumulated. Calcifications around the heart may be seen w/constrictive pericarditis.
- ECG varies w/the evolutionary stage of pericarditis
  - Acute phase: diffuse ST-segment elevations (particularly evident in the precordial leads), which can be distinguished from acute MI by absence of reciprocal ST-segment depression in oppositely oriented leads (reciprocal ST-segment depression may be seen in aVR and V1), ↑ ST segments concave upward, absence of Q waves
  - Intermediate phase: return of ST segment to baseline, and T wave inversion in leads previously showing ST-segment elevation
  - Late phase: resolution of the T wave changes

**Etiology**
- Idiopathic (possibly postviral). In 90%, cause is either viral or unknown (idiopathic).
- Infectious (viral, bacterial [1%-2%], tuberculous [4%], fungal, amebic, toxoplasmosis)
- Collagen-vascular disease (SLE, RA, scleroderma, vasculitis, dermatomyositis): 3%-5% of cases
- Drug-induced lupus syndrome: procainamide, hydralazine, phenytoin, isoniazid, rifampin, doxorubicin, mesalamine
Diseases

Acute MI
Trauma or post-traumatic
Post MI (Dressler’s syndrome)
Post pericardiectomy
Post mediastinal irradiation (e.g., pts w/Hodgkin’s disease)
Uremia
Sarcoidosis
Neoplasm (primary or metastatic [breast, lung, leukemia, lymphoma]): 7% of cases
Leakage of aortic aneurysm in pericardial sac
Familial Mediterranean fever
RF
Other: anticoagulants, amyloidosis, ITP

Treatment

NSAIDs
Prednisone 30 mg bid for severe forms of acute pericarditis (before use of prednisone, tuberculous pericarditis must be excluded)
Colchicine 0.6 mg bid may be used as an alternative in pts intolerant of NSAIDs and corticosteroids.
Consider ventricular rate control w/verapamil or diltiazem because of the propensity for AF.
Close observation of pts for signs of cardiac tamponade
Avoidance of anticoagulants (↑ risk of hemopericardium)
Treat underlying cause of pericarditis.

298 PERIPHERAL ARTERIAL DISEASE (PAD)

Definition
Stenotic, occlusive, and aneurysmal diseases of the aorta and its branch arteries, exclusive of the coronary arteries. This section deals specifically w/the arteries of the LEs.

Diagnosis

H&P

50% of the pts w/PAD are asymptomatic.
33% present w/intermittent claudication (aching or cramping leg pain brought on by exertion and relieved w/rest).

Other manifestations:
- Painful cramping in buttocks, hip, or leg that occurs while walking but goes away while resting
- Diminished pedal pulses
- Bruits heard over the distal aorta, iliac or femoral arteries
- Changes in skin color, especially on feet (rubor w/prolonged capillary refill on dependency or delayed pallor)
- Cool skin temperature
- Trophic changes of hair loss and muscle atrophy
- Nonhealing ulcers, necrotic tissue, and gangrene
- Weakness, numbness, or a feeling of heaviness in legs
- Aching or burning in toes and feet during rest and especially while lying flat, which may be a sign of ischemia and more serious PAD

Workup

Measurement of BP in both arms and notation of any asymmetry
Palpation and recording of carotid pulses, upstroke, amplitude, and presence of bruits
Auscultation and palpation of abd for bruits, aortic pulsation, and diameter
Palpation of brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Pulse intensity should be recorded as follows: 0, absent; 1, diminished; 2, nl; 3, bounding.
Auscultation of femoral arteries for the presence of bruits
Feet should be inspected for color, temperature, and integrity of the skin.
Findings suggestive of severe PAD: hair loss, trophic skin changes, and hypertrophic nails—should be sought and recorded.
In pts w/sx of intermittent claudication, the ankle-brachial index (ABI) should be measured after exercise (especially if the resting study is nl).
The ABI is calculated by dividing the highest ankle systolic pressure in either the dorsalis pedis or posterior tibial artery by the highest systolic pressure from either arm.

- A dx of PAD is based on the presence of limb sx or a low ABI.
- The severity of PAD is based on the ABI at rest and during treadmill exercise (1-2 mph, 5 min, or sx limited). It is classified as follows:
  - Mild: ABI at rest 0.71-0.90 or ABI during exercise 0.50-0.90
  - Moderate: ABI at rest 0.41-0.70 or ABI during exercise 0.20-0.50
  - Severe: ABI at rest <0.40 or ABI during exercise <0.20

**Labs**
- Lipid profile, FBS

**Imaging**
- CTA or MRA can be used to localize and quantify arterial stenosis.
- Catheter-based digital-subtraction angiography (DSA) remains the gold standard for visualizing the arterial anatomy before revascularization.

**Etiology**
- The primary cause of PAD is atherosclerosis: atherosclerotic lesions lead to stenosis of peripheral vessels and inability to supply oxygenated blood to meet the demand of limb muscles.

**Treatment**
- Smoking-cessation programs, diet counseling, and weight-loss programs
- Management of HTN w/goal <140/90 or <130/80 if the pt has diabetes or chronic renal disease
- Tight glycemic control: HbA1c <6.5% in diabetics
- Control dyslipidemia: goal for LDL <70 in very high risk pts
- ASA 81 mg qd for secondary prevention
- Clopidogrel 75 mg qd in pts who cannot tolerate ASA
- Cilostazol 100 mg bid is effective for intermittent claudication.
- Revascularization (surgery or percutaneous transluminal angioplasty) in pts w/claudication that limits their lifestyle and is unresponsive to exercise and pharmacologic Rx
- Endovascular Rx is preferred in pts who are ≤50 yr of age because they have a higher risk of graft failure after surgical Rx than do older pts.
- Endovascular intervention is not indicated if there is no significant pressure gradient across a stenosis even after augmentation of flow w/vasodilators. It is also not indicated as prophylactic Rx in an asymptomatic pt w/LE PAD.
- Primary stent placement is not recommended in the femoral, popliteal, or tibial arteries.

299 PERIPHERAL NERVE DYSFUNCTION (PERIPHERAL NEUROPATHY)

**Definitions**
- **Peripheral neuropathy:** any disorder involving the peripheral nerves.
- **Polyneuropathy (symmetric polyneuropathy):** generalized process resulting in widespread and symmetric effects on the PNS.
- **Focal or multifocal neuropathy (mononeuropathy, mononeuropathy multiplex):** local involvement of one or more individual peripheral nerves.
- **Paresthesia:** spontaneous aberrant sensation (e.g., pins and needles).

**Diagnosis**

**Hx**
- FHx of neuropathies: r/o hereditary neuropathies
- Current and past employment: r/o exposure to toxic agents
- Current or recent meds: r/o neuropathy secondary to drugs
- Any systemic disease such as diabetes, renal failure, hypothyroidism
- Ethanol abuse: r/o alcoholic neuropathy; diabetes and alcoholism are the most common causes of peripheral neuropathy in the U.S.
- Any special diets (e.g., food faddists): r/o nutritional deficiencies
- H/o trauma: r/o compression entrapment neuropathies
- Duration and progression of sx
- Risk factors for AIDS
- H/o tick bite or ECM: Lyme disease
PERIPHERAL NERVE DYSFUNCTION

**PE**
- Define the type of neuropathy present.
- Sensory vs. motor vs. mixed
- Number of nerves involved (e.g., mononeuropathy, polyneuropathy, mononeuropathy multiplex)
- Determine territory of neurologic deficit.
- Evaluate DTRs: ↓ in root and peripheral nerve disease.

**Labs**
- CBC, electrolytes, BUN, Cr, glucose, LFTs, CPK, Ca, Mg, phosphate; HIV, Lyme titer in pts w/suggestive hx
- If toxic neuropathy suspected: heavy metal screening; in suspected lead poisoning, blood lead concentration, urinary tests for coproporphyrin and δ-aminolevulinic acid, and bone marrow aspirates (to evaluate the presence of basophilic stippling in normoblasts)
- TSH: r/o hypothyroidism.
- Vitamin B\textsubscript{12} and RBC folate: r/o nutritional deficiencies
- ANA, serum ACE level, VDRL, serum and urine protein IEP
- LP: in suspected GBS
- Nerve bx (usually sural nerve)

**Imaging**
- CXR: r/o sarcoidosis, lung cancer
- X-ray of involved limb: in suspected trauma or peripheral nerve compression
- EMG: spontaneous fibrillation potentials and positive sharp waves at rest in neurogenic lesions

**Etiology**
- Hereditary neuropathies
  - Charcot-Marie-Tooth syndrome
  - Others: Dejerine-Sottas disease, Refsum’s disease, Riley-Day syndrome
- Acquired neuropathies
  - DM
  - Myxedema
  - Uremia
  - Sarcoïdosis
  - Alcohol
  - Neoplasms
  - Nutritional deficiencies: thiamine, folic acid, vitamin B\textsubscript{12}
  - Others: collagen vascular diseases, amyloidosis, MM
- Guillain-Barré neuropathy
- Toxic neuropathies. Drugs: chloramphenicol, lithium, isoniazid (INH), pyridoxine, nitrofurantoïn, disulfiram, dapsone, ethionamide, cisplatin, vincristine, metronidazole, gold, hydralazine, amiodarone, phenytoïn, penicillamine, indomethacin, amphotericin B, amïtriptylïne, sulfonylïmides, colchïcine, antiretrovirals (didanosïne, stavudïne, zalcïtabïne, interferon alfa), cimetiïdine
- Toxic chemicals: lead, arsenïc, cyanïde, thallïum, carbon disulïfide, mercury, organophosphates, trichlororoïlïene
- Neuropathies associated w/infection: leprosy, herpes zoster, diphïtheria, Lyme disease, HIV infection
- Entrapment neuropathy (e.g., carpal tunnel syndrome)

**Treatment**
- Stop offending agents.
- Specific treatment (e.g., combination w/BAL and CaEDTA) in pts w/lead poisoning, plasmapheresis followed by ↓-dose prednisone in AIDS pts w/inflammatory demyelinating neuropathy, administration of oral pyridoxine (50 mg bid) to prevent INH neuropathy, vitamin B\textsubscript{12} supplementation in vitamin B\textsubscript{12} deficiency
- Consider immunoglobulin Rx if neurotherapy is immune mediated.
PERITONITIS, BACTERIAL (SECONDARY)

Definition
Peritonitis refers to abd pain secondary to peritoneal inflammation. Secondary peritonitis is a localized (abscess) or diffuse peritonitis originating from a defect in abd viscus.

Diagnosis

H&P
- Acute abd pain, abd distention and ascites, abd rigidity, rebound and guarding, fever, chills, ↓ bowel sounds, hypotension and tachycardia, tachypnea, dyspnea
- If pt is hemodynamically unstable, immediate diagnostic laparotomy should be performed in lieu of adjuvant diagnostic studies.

Labs
- CBC: leukocytosis, left shift, anemia
- SMA7: electrolyte imbalances, kidney dysfunction
- LFT: ascites secondary to liver disease, cholelithiasis
- Amylase: pancreatitis
- Blood cultures: bacteremia, sepsis
- Peritoneal cultures: infectious etiology
- ABGs: respiratory vs. metabolic acidosis
- Ascitic fluid analysis: exudate vs. transudate
- U/A and C&S: UTI
- Cervical cultures for gonorrhea and Chlamydia
- Urine/serum hCG

Imaging
- Abd series: free air secondary to perforation, small or large bowel dilation secondary to obstruction, identification of fecalith
- CXR: elevated diaphragm, pneumonia
- Pelvic/abd U/S: abscess formation, abd mass, intrauterine vs. ectopic pregnancy; identify free fluid suggestive of hemorrhage or ascites
- CT: mass, ascites

Etiology
- Microbiology: most common are gram-negative bacteria (E. coli, Enterobacter, Klebsiella, Proteus), gram-positive bacteria (enterococci, streptococci, staphylococci), anaerobic bacteria (Bacteroides, Clostridium), and fungi.
- Acute perforation peritonitis: GI perforation, intestinal ischemia, pelvic peritonitis, and other forms
- Postoperative peritonitis: anastomotic leak, accidental perforation, and devascularization
- Post-traumatic peritonitis: after blunt or penetrating abd trauma

Treatment
- Surgery to correct underlying pathologic process (e.g., control hemorrhage, correct perforation, drain abscess)
- Broad-spectrum abx:
  - Single agent: ceftriaxone 1-2 g IV q24h, cefotaxime 1-2 g IV q4-6h
  - Multiple agents:
    - Ampicillin 2 g IV q4-6h; gentamicin 1.5 mg/kg/day; clindamycin 600-900 mg IV q8h
    - Ampicillin 2 g IV q4-6h; gentamicin 1.5 mg/kg/day; metronidazole 500 mg IV q6-8h
- Pain control: morphine or meperidine as needed (hold until dx confirmed)

PERITONITIS, SPONTANEOUS (PRIMARY, SBP)

Definition
Bacterial peritonitis w/o an evident source of infection in a pt w/ascites.

Diagnosis
- Ascitic fluid analysis:
  - PMN cell count >250/mm³ in ascitic fluid: most sensitive and specific test for SBP if >500/mm³
• Presence of bacteria on initial Gram stain of ascitic fluid
• Lactic acid (lactate) >32/dL
• pH <7.31 or arterial/ascitic fluid pH >0.1
• Protein <1 g/dL
• Glucose >50 mg/dL
• LDH <225 mU/mL
• Positive culture of peritoneal fluid

Major distinguishing factors between SBP and secondary peritonitis (perforation of bowel wall):
• Presence of free air on abd x-ray films in secondary peritonitis
• Common presence of multiple organisms and anaerobes in ascitic fluid in secondary peritonitis
• Analysis of ascitic fluid in secondary peritonitis reveals leukocyte count >10,000/mm³, LDH >225 mU/mL, protein >1 g/dL, and glucose <50 mg/dL.
• Repeated paracentesis after 48 hr of appropriate abx Rx will reveal a significant ↓ in ascitic fluid PMN count in pts w/SBP and no ↓ in pts w/a secondary bacterial peritonitis.

Etiology

■ SBP usually occurs as a complication of hepatic ascites. The following mechanisms may account for bacterial seeding of the ascitic fluid:
  • Hematogenous transmission
  • Direct transmural passage after mucosal drainage (ischemia, edema)
  • Bowel perforation after paracentesis (uncommon)
• Infecting organisms: E. coli, streptococcus group D, S. pneumoniae and S. viridans, Enterobacter, Pseudomonas, Klebsiella

Treatment

■ Cefotaxime 2 g IV q8h or ceftriaxone 2 g IV q24h in pts w/nl renal function; treatment duration generally 7-10 days; oral quinolone Rx (ofloxacin 100-800 mg/day) may be an acceptable alternative.

Clinical Pearl

■ SBP is associated w/hepatic ascites in 8%-25% of cases of ascites. TMP-SMZ (Bactrim DS, Septra DS) one tablet 5x/wk and ciprofloxacin 750 mg PO q wk are effective for the prevention of SBP in pts w/cirrhosis.

302 PHEOCHROMOCYTOMA

Definition

Catecholamine-producing tumors that originate from chromaffin cells of the adrenergic system. They generally secrete both norepinephrine and epinephrine, but norepinephrine is usually the predominant amine.

Diagnosis

H&P

■ HTN: sustained (55%) or paroxysmal (45%)
■ Headache (80%): paroxysmal, described as “pounding” and severe
■ Palpitations (70%): w/ or w/o tachycardia
■ Hyperhidrosis (60%): most evident during paroxysmal attacks of HTN
■ PE may be entirely nl if done in a sx-free interval; during a paroxysm, there is ↑↑ in both systolic and diastolic pressure, profuse sweating, visual disturbances (caused by hypertensive retinopathy), dilated pupils (secondary to catecholamine excess), paresthesias in the LEs (caused by severe vasoconstriction), tremor, tachycardia.

Labs

■ Plasma-free metanephrines: test of first choice for dx. Plasma concentrations of normetanephrines >2.5 pmol/mL or metanephrine levels >1.4 pmol/mL indicate a pheochromocytoma w/nearly 100% specificity.
■ 24-hr urine collection for metanephrines (100% sensitive): ↑ metanephrines
■ The clonidine suppression test: useful for distinguishing between ↑ levels of plasma norepinephrine caused by release from sympathetic nerves and those caused by release from a pheochromocytoma. A ↓ (<50%) in plasma
norepinephrine levels after clonidine administration is nl, whereas persistent ↑ indicates pheochromocytoma.

**Imaging**
- Abd CT (88% sensitivity): useful in locating pheochromocytomas >0.5 inch in diameter (90%-95% accurate)
- MRI: pheochromocytomas demonstrate a distinctive MRI appearance (100% sensitivity).
- Scintigraphy w/¹³¹I-MIBG (100% sensitivity): this norepinephrine analogue localizes in adrenergic tissue; useful in locating extra-adrenal pheochromocytomas.
- 6-[¹⁸F]Fluorodopamine PET: used when biochemical test results are + but other imaging cannot locate the tumor.

**Treatment**
Laparoscopic removal of the tumor (surgical resection for both benign and malignant disease):
- Preoperative stabilization w/combination of phenoxybenzamine, β-blocker, metyrosine, and liberal fluid and salt intake starting 10-14 days before surgery
- HTN crisis preoperatively and intraoperatively controlled w/phentolamine 2-5 mg IV q1-2h PRN or nitroprusside used in combination w/β-adrenergic blockers

**Clinical Pearls**
- 10% of pheochromocytomas are familial.
- Screen for pheochromocytoma in pts w/malignant HTN, poor response to anti-HTN Rx, and paradoxical HTN response.

### PINWORMS

**Definition**
Noninvasive infestation of the intestinal tract by *Enterobius vermicularis*, a helminth of the nematode family.

**Diagnosis**
*H&P*
- Perianal itching is most common reported sx, w/scratching leading to excoriation and sometimes secondary infection.
- Most infested pts are asymptomatic.

*Labs*
- Identification of adult worms or eggs on transparent tape placed on the perianal skin on awakening (note: 5 consecutive – tests r/o dx)

**Etiology**
- Humans are the only host for this worm. Infestation is by fecal-oral route; ingested eggs hatch in the stomach, and the larvae migrate to the colon, where they mature. Gravid female worms migrate to the perianal skin at night, lay their eggs there, and die. The eggs cause itching; scratching causes egg deposition under fingernails, from which they can contaminate food or lead to autointection.

**Treatment**
- Single dose of mebendazole (100 mg PO) w/repeated dose given after 2 wk
- Single dose of albendazole (400 mg PO) w/second dose given 2 wk later is also highly effective.
- Pyrantel pamoate (11 mg/kg up to 1 g) can protect against *Enterobius vermicularis*. It is available as a suspension and has min. toxicity (mild transient GI sx, headache, drowsiness). A repeated dose after 2 wk is recommended because of the frequency of reinfection and autoinfection.
- Other infected family members, classmates, or residents of long-term care facilities should be treated at the same time as the index case.

### PNEUMONIA, ASPIRATION

**Definition**
Lung infection caused by bacterial organisms aspirated from nasopharyngeal space.
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Diagnosis
- CXR: bilateral, diffuse, patchy infiltrates and posterior segment upper lobes
- Aspiration of pneumonias > several days in duration may reveal necrosis (especially community-acquired anaerobic pneumonias) and even cavitation with/air-fluid levels, indicating lung abscess.

Etiology
Complex interaction of etiologic factors, ranging from chemical (often acid) pneumonitis after aspiration of sterile gastric contents (generally not requiring abx treatment) to bacterial aspiration.

Community-Acquired Aspiration Pneumonia
- Generally results from predominantly anaerobic mouth bacteria (anaerobic and microaerophilic streptococci, fusobacteria, gram-positive anaerobic non–spore-forming rods), Bacteroides species (melaninogenicus, intermedius, oralis, ureolyticus), Haemophilus influenzae, and Streptococcus pneumoniae
- Rarely caused by Bacteroides fragilis or Eikenella corrodens
- High-risk groups: elderly; alcoholics; IV drug users; pts who are obtunded; those with/ophagel disorders, seizures, poor dentition, or recent dental manipulations; stroke victims

Hospital-Acquired Aspiration Pneumonia
- Often occurs among elderly pts and others w/diminished gag reflex; those w/NG tubes, intestinal obstruction, or ventilator support; and especially those exposed to contaminated nebulizers or unsterile suctioning
- High-risk groups: seriously ill hospitalized pts (especially pts w/coma, acidosis, alcoholism, uremia, DM, NG intubation, or recent antimicrobial Rx, who are frequently colonized w/gram-negative rods); pts undergoing anesthesia; those w/strokes, dementia, swallowing disorders; the elderly; and those receiving antacids or H₂ blockers (but not sucralfate)
- Hypoxic pts receiving concentrated O₂ have diminished ciliary activity, encouraging aspiration
- Causative organisms:
  - Anaerobes listed previously, although gram-negative aerobes (60%) and gram-positive aerobes (20%) predominate in many studies.
  - E. coli, P. aeruginosa, S. aureus, Klebsiella, Enterobacter, Serratia, and Proteus spp. H. influenzae, S. pneumoniae, Legionella, and Acinetobacter spp. sporadic pneumonias in % of cases
  - Fungi, including Candida albicans, in <1%

Treatment
- Acute aspiration of acidic gastric contents w/o bacteria may not require abx Rx.
- Community-acquired anaerobic aspiration pneumonia: levofoxacin 500 mg qd or ceftriaxone 1-2 g/day
- Nursing home aspirations: levofoxacin 500 mg qd or piperacillin-tazobactam 3.375 g q6h or ceftazidime 2 g q8h
- Hospital-acquired aspiration pneumonia:
  - Piperacillin-tazobactam 3.375 g IV q6h, or clindamycin 450-900 mg IV q8h, or cefoxitin 2 g IV q8h
  - Knowledge of resident flora in the microenvironment of the aspiration within the hospital is crucial to intelligent abx selection; consult infection control nurses or hospital epidemiologist.
  - Confirmed Pseudomonas pneumonia should be treated w/ antipseudomonal β-lactam agent plus an AG until antimicrobial sensitivities confirm that less toxic agents may replace AG.
  - Do not use metronidazole alone for anaerobes.

305 PNEUMONIA, BACTERIAL

Definition
Infection involving the lung parenchyma.
Diagnosis

**H&P**
- Fever, tachypnea, chills, tachycardia, cough
- Presentation varies with the cause of pneumonia, pt’s age, and clinical situation:
  - Streptococcal pneumonia: high fever, shaking chills, pleuritic chest pain, cough, and copious production of purulent sputum
  - Elderly or immunocompromised hosts: may present with only min. sx (e.g., low-grade fever, confusion)
  - Crackles and ↓ breath sounds
  - Percussion dullness: pleural effusion

**Imaging**
- Segmental lobe infiltrate: pneumococcal pneumonia
- Diffuse infiltrates: *L. pneumophila*, *M. pneumoniae*, viral pneumonias, *P. carinii*, miliary TB, aspiration, aspergillosis

**Treatment**
- Macrolides (azithromycin or clarithromycin) or levofloxacin for empiric outpatient treatment; cefotaxime or a β-lactam/β-lactamase inhibitor can be added in pts w/more severe presentation who insist on outpatient Rx. Duration of treatment: 7-14 days.
- In pts admitted to general med ward: second- or third-generation ceph (ceftriaxone, cefotaxime, cefotaxime, or cefuroxime) + a macrolide (azithromycin or clarithromycin) or doxycycline. An antipseudomonal quinolone (levofloxacin or moxifloxacin) may be substituted in place of the macrolide or doxycycline.
- Empiric Rx in ICU pts: IV β-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) + an IV quinolone (levofloxacin, moxifloxacin) or IV azithromycin
- In hospitalized pts at risk for *P. aeruginosa* infection: antipseudomonal β-lactam (cefepime or piperacillin-tazobactam) + an AG + an antipseudomonal quinolone or macrolide
- In pts w/suspected MRSA: vancomycin or linezolid

**Clinical Pearl**
Causes of slowly resolving or nonresolving pneumonia:
- Difficult-to-treat infections: viral pneumonia, *Legionella*, pneumococci, or staphylococci w/impaired host response; TB, fungi
- Neoplasm: lung, lymphoma, metastasis
- CHF
- PE
- Immunologic or idiopathic: Wegener’s granulomatosis, pulmonary eosinophilic syndromes, SLE
- Drug toxicity (e.g., amiodarone)

306 PNEUMONIA, MYCOPLASMA

**Definition**
Infection of the lung parenchyma caused by *Mycoplasma pneumoniae*.

**Diagnosis**

**H&P**
- Clinical presentation: nonexudative pharyngitis (common), rhonchi or rales, w/o evidence of consolidation (common) in lower lung zones; associated w/bullous myringitis (perhaps no more frequently than in other pneumonias)

**Imaging**
- CXR: predilection for lower lobe involvement (upper lobes in <25%), w/radiographic abnormalities frequently out of proportion to those on PE; small pleural effusions in 30% of pts

**Treatment**
- Azithromycin (500 mg initially, then 250 mg qd for 4 days) or clarithromycin (500 mg bid). Levaquin is alternative agent for treatment but should not be used in young children.
307 PNEUMONIA, *PNEUMOCYSTIS JIROVECI* (PJP)

**Definition**
Serious respiratory infection caused by the fungal or protozoal organism *Pneumocystis jiroveci*.

**Diagnosis**

**H&P**
- Fever, cough, SOB present in almost all cases
- Lungs frequently clear to auscultation, although rales occasionally present

**Labs**
- HIV serology
- Sputum examination for cysts of PJP and to exclude other pathogens
- Bronchoscopy w/BAL or lung bx for dx if sputum examination is negative or equivocal

**Imaging**
- CXR
- Gallium scan: diffuse uptake (suggestive but not dx)

**Treatment**
- TMP-SMZ (15-20 mg/kg trimethoprim and 75-100 mg/kg sulfamethoxazole qd) PO or IV per day divided and given q6-8h
- Pentamidine (4 mg/kg IV qd)
- Either regimen w/prednisone (40 mg PO bid):
  - If arterial oxygen pressure <70 mm Hg
  - If arterial-alveolar oxygen pressure difference >35 mm Hg
  - Dose tapered to 20 mg bid after 5 days and 20 mg qd after 10 days
  - Rx continued for 3 wk
- Alternative Rx available for pts unable to tolerate conventional Rx:
  - Dapsone/trimethoprim
  - Clindamycin/primaquine
  - Atovaquone
- Chronic Rx:
  - After completion of Rx, lifelong prophylaxis should be maintained w/TMP-SMZ (one single-strength tablet PO qd or double-strength 3×/wk).
  - Pts intolerant of this Rx should be treated w/dapsone (50 mg PO qd) + pyrimethamine (50 mg PO q wk) + leucovorin (25 mg PO q wk).
  - Inhaled pentamidine (300 mg monthly by standardized nebulizer) is less effective and is reserved for pts intolerant of other forms of prophylaxis.
  - The same approach is taken to all HIV-infected pts w/CD4 lymphocyte counts <200-250/mm³ or <20% of the total lymphocyte count because of ↑ risk of *Pneumocystis* pneumonia.

308 PNEUMOTHORAX

**Definition**
A spontaneous pneumothorax (SP) is defined as the accumulation of air into the pleural space, collapsing the lung. This can be primary SP (i.e., w/o any obvious underlying lung disease) or secondary SP (i.e., w/underlying lung disease).

**Diagnosis**

**H&P**
- Sudden onset of pleuritic chest pain (90%), which often becomes dull after a few hours
- Dyspnea (80%), which often resolves within 24 hr, despite persistence of pneumothorax
- Cough (10%)
- Asymptomatic (5%), may take up to 7 days to come to medical attention
- Tachycardia
- ↓ Breath sounds
- ↓ Tactile fremitus
- Hyperresonance

**Labs**
- ABGs: hypoxemia and hypocapnia secondary to hyperventilation
Imaging
- CXR
  - Identification of white visceral pleural line w/absence of vessel markings peripheral to this line helps differentiation from mimicking conditions like an overlying skin fold.
  - The left lateral decubitus position is the most sensitive, and the supine position the least sensitive.
  - As little as 50 mL of air can be detected on upright film, and a lateral width of 1 cm corresponds to 10% pneumothorax.
  - Tension pneumothorax is suspected w/contralateral tracheal and mediastinal deviation and ipsilateral flattening or inversion of the diaphragm.
- CT chest: done in suspected but difficult-to-visualize pneumothoraces or to differentiate from large subpleural bullae

Etiology
- In primary SP, rupture of small blebs, usually located near the apex of the upper lobes, is a common cause.
- In secondary SP, COPD is the most common cause, but it can also be associated w/pneumonia, bronchogenic carcinoma, mesothelioma, sarcoidosis, TB, CF, and many other lung diseases.

Treatment
- 100% O₂ administration ↓ the partial pressure of nitrogen in pleural capillaries and consequently quadruples the rate of pneumothorax absorption.
- Observation alone is acceptable in the asymptomatic pt w/<15% pneumothorax, once a repeated CXR demonstrates stability of the condition; but it requires close outpatient monitoring.
- Aspiration is used only in a stable pneumothorax and can be done with a thoracentesis catheter, introduced in the second intercostal space midclavicular line attached to a 3-way stopcock and a large syringe. Films are repeated immediately after aspiration and again in 24 hr. If the lung fails to expand after 4 L, surgical exploration should be considered.
- If there is improvement but not complete resolution of pneumothorax after the aspiration, the catheter can be attached to a Heimlich (one-way) valve to allow outpatient management of this condition.
- Chest tube insertion: in pts w/primary SP who fail observation and simple aspiration and for all pts w/secondary SP.
- There is no firm conclusion on the optimal treatment (simple aspiration vs. chest tube insertion) for a first episode of primary SP. Studies suggest that shorter hospital stay can be achieved w/the aspiration technique, but there is a potential risk of lung laceration.
- Air leak for 3 days after tube thoracostomy insertion suggests the presence of bronchopleural fistula. Most will resolve w/conservative measures only, including continued observation; ↑ the suction applied to pleural space to 35 cm H₂O or reposition the tube.
- The absence of visible leak does not guarantee that the leak has resolved because air might bubble out intermittently. Therefore, chest tube should be clamped for 24 hr before removal.
- Thoracoscopy or video-assisted thoracoscopy (VAT): indicated in pts who have persistent air leak for 7 days. Application of Heimlich valve to chest tube or intrabronchial bronchoscopic instillation of fibrin glue to occlude fistula should be considered in poor surgical candidates.

Clinical Pearls
- Multiple techniques have been used to prevent recurrence, including pleural pleurectomy, laser abrasion of parietal pleura, intrapleural instillation of sclerosing agents, and pleural abrasion w/dry gauze. The overall recurrence rates are estimated at <5%.
- The current technique of choice is VAT, but its timing in the prevention of primary SP recurrence remains controversial. Most recommend definitive management after the first recurrence. However, ↑ risk occupations such as divers and pilots should be considered for surgery after first
Diseases

arteries, small to characterized involvement of medium-sized arteries. The recurrence rates for the instillation of sclerosing agents (minocycline 5 mg/kg in 50 mL of NS or doxycycline 500 mg in 50 mL of NS) are > video-assisted thoracoscopic surgery (VATS). Therefore, this should be reserved for pts who are poor surgical candidates. Open thoracotomy is done in pts who fail VATS or where VATS is not available.

509 POLYARTERITIS NODOSA (PAN)

Definition
Vasculitic syndrome involving medium-sized to small arteries, characterized histologically by necrotizing inflammation of the arterial media and inflammatory cell infiltration.

Diagnosis
H&P
- Typical presentation is subacute, w/the onset of constitutional sx during weeks to months.
- Weight loss, N/V
- Testicular pain or tenderness
- Myalgias, weakness, or leg tenderness
- Neuropathy (mononeuritis multiplex), footdrop
- Livedo reticularis, ulceration of digits, abd pain pc, hematemesis, hematochezia, HTN, asymmetric polyarthritis (tending to involve large joints of LEs); true synovitis occurs only in a minority of pts.
- Fever may be present (polyarteritis nodosa is often cause of FUO) and can range from intermittent, low-grade fevers to high fevers w/chills.
- Tachycardia is common and often striking.

Labs
- ↑ BUN, ↑ Cr, + HBV or hepatitis C
- ↑ ESR, ↑ CRP, ↓ Hb/Hct, ↑ platelets, eosinophilia, proteinuria, hematuria
- Bx of small or medium-sized artery of symptomatic sites (muscle, nerve) is >90% specific. Bx of gastrocnemius muscle and sural nerve is commonly performed.
- ANA and RF are −; however, low, nonspecific titers may be detected.

Imaging
- Visceral angiography will reveal aneurysmal dilation of the renal, mesenteric, or hepatic arteries.

Diagnostic Criteria
The presence of any 3 of the following 10 items allows the dx of polyarteritis nodosa w/a sensitivity of 82% and a specificity of 86%:
- Weight loss >4 kg
- Livedo reticularis
- Testicular pain or tenderness
- Myalgias, weakness, or leg tenderness
- Neuropathy
- Diastolic BP >90 mm Hg
- ↑ BUN or Cr
- Positive test result for HBV
- Arteriography revealing small or large aneurysms and focal constrictions between dilated segments
- Bx of small or medium-sized artery containing WBC

Treatment
- Prednisone 1-2 mg/kg/day; cyclophosphamide in refractory cases

Clinical Pearl
- The 5-yr survival is <20% in untreated pts. Treatment w/corticosteroids ↑ survival to 50%. Use of both corticosteroids and immunosuppressive drugs may ↑ 5-yr survival >80%. A poor prognostic sign is severe renal or GI involvement.
**310 POLYCYSTIC KIDNEY DISEASE (AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE, ADPKD)**

**Definition**
Hereditary disorder characterized by the formation of cysts in the cortex and medulla of both kidneys. A person is considered to have ADPKD if ≥2 cysts are noted in one or both kidneys and there is a family member w/ADPKD.

**Diagnosis**

**H&Q**
- Usually presents in the third to fourth decade of life
- Pain (abd, flank, or back)
- Palpable flank mass
- HTN
- Headache
- Nocturia
- Hematuria
- Nephrolithiasis (20%)
- UTI

**Labs**
- ↑ Hgb/Hct due to ↑ secretion of erythropoietin from functioning renal cysts
- U/A: hematuria, WBC casts in pyelonephritis, or proteinuria (seldom >1 g/24 hr)
- Serum erythropoietin level
- Pts w/ a strong + FHx of ADPKD and no cysts detected by imaging studies can undergo genetic linkage analysis.

**Imaging**
- Renal U/S: can detect cysts from 1-1.5 cm
- Abd CT: can detect cysts as small as 0.5 cm
- MRI: more sensitive, can distinguish renal cell carcinomas from simple cysts

**Etiology**
- 90% of cases are inherited as an autosomal dominant trait.
- Spontaneous mutations occur in 10% of cases.

**Treatment**
- Avoidance of physical contact sports
- Kidney infections: should be treated w/abx that penetrate the cyst (e.g., TMP-SMZ 1 tablet PO bid or ciprofloxacin 250 mg PO bid)
- ACEIs and CCBs for HTN
- Dialysis and renal transplantation for ESRD
- Cystic decompression in pts w/intractable pain caused by enlarging cysts

**Clinical Pearls**
- 50% of pts will progress to ESRD.

**311 POLYCYTHEMIA VERA**

**Definition**
Chronic myeloproliferative disorder characterized mainly by erythrocytosis (↑ in RBC mass).

**Diagnosis**

**Clinical Presentation**
Sx associated w/↑ blood volume and viscosity or impaired platelet function:
- Impaired cerebral circulation: headache, vertigo, blurred vision, dizziness, TIA, CVA
- Fatigue, poor exercise tolerance
- Pruritus, particularly after bathing (caused by overproduction of histamine)
- Bleeding: epistaxis, UGI bleeding (↑ incidence of PUD)
- Abd discomfort secondary to splenomegaly; hepatomegaly may be present
- Hyperuricemia may result in nephrolithiasis and gouty arthritis.

**PE**
- Facial plethora, congestion of oral mucosa, ruddy complexion
- Enlargement and tortuosity of retinal vein
- Splenomegaly (>75% of pts)
**POLYMYALGIA RHEUMATICA (PMR)**

**Definition**
Clinical syndrome predominantly involving individuals >50 yr and characterized by pain and stiffness involving mainly the shoulders, pelvic girdle musculature, and torso.

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**FIGURE 3-40.** Diagnostic algorithm for polycythemia vera.

**Labs**
- ↑ RBC count (>6 million/mm³), ↑ Hgb (>18 g/dL in men, >16 g/dL in women), ↑ Hct (>54% in men, >49% in women)
- ↑ WBC (often w/basophilia); thrombocytosis in the majority of pts
- Leukocyte alk phos, serum vitamin B₁₂, and uric acid levels
- Serum erythropoietin level. Serum erythropoietin level is the best initial test to dx PV (Fig. 3-40).
- JAK2 V617F mutation test w/PCR assay. The JAK2 mutation is found in >95% of pts w/PV. The presence of the JAK2 mutation is sufficient for the diagnosis of PV in pts w/↑ Hct (>52% in men or >48% in women) in absence of coexisting secondary erythrocytosis.
- Bone marrow exam: RBC hyperplasia and absent iron stores

**Treatment**
Phlebotomy to keep Hct <45% in men and <42% in women. Additional options:
- Hydroxyurea
- Interferon alfa-2b
- Treatment of pruritus w/antihistamines, control of hyperuricemia w/ allopurinol, reduction of gastric hyperacidity w/antacids of H₂ blockers, low-dose ASA to treat vasomotor sx and thrombotic complications in pts w/o bleeding diathesis

**Clinical Pearls**
- The median survival time w/o treatment is 6-18 mo after dx; phlebotomy extends the average survival time to 12 yr.
- Prognosis is worse in pts >60 yr of age and those who have h/o thrombosis.

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**POLYMYALGIA RHEUMATICA (PMR)**

**Definition**
Clinical syndrome predominantly involving individuals >50 yr and characterized by pain and stiffness involving mainly the shoulders, pelvic girdle musculature, and torso.
Diagnosis
Dx is based on clinical presentation and ↑ ESR (≥40 mm/hr), although the latter is not essential for the diagnosis (>20% of pts w/PMR have a nl ESR at time of dx).

H&P
- Symmetric polymyalgias and arthralgias involving back, shoulder, neck, and pelvic girdle muscles; duration is generally >1 mo
- Constitutional sx (fever, malaise, weight loss)
- Headache in pts w/coexisting giant cell arteritis
- Sx worse in the morning (difficulty getting out of bed) and at night
- Muscle strength nl
- Crescendo of sx during several weeks or months
- Depression or weight loss

Labs
- ↑ ESR, mild anemia

Treatment
- Prednisone, 10-20 mg/day
  - Dramatic relief of sx within 48-72 hr confirms dx.
  - Failure to improve within 1 wk suggests other dx: fibromyalgia, polymyositis, viral myalgias, hypothyroidism, depression, RA, occult neoplasm, or infection.
- The corticosteroid dosage is then gradually tapered during several months on the basis of repeated clinical observation and serial measurements of ESR.
- In pts w/min. sx, NSAIDs may be used instead of corticosteroids.

Clinical Pearls
- In general, temporal artery bx is not indicated in pts w/pure PMR (i.e., in the absence of giant cell arteritis signs and sx).
- A baseline bone density study in female pts is recommended because of ↑ risk of osteoporosis w/prolonged prednisone use.

313 PORTAL VEIN THROMBOSIS
Diagnosis
H&P
- Portal vein thrombosis results in portal HTN leading to esophageal and GI varices. Upper GI hemorrhage (hematemesis or melena) due to esophageal varices can occur.
- If abd pain is present, mesenteric venous thrombosis should be suspected.

Imaging
- Abd U/S or MRI may show the portal vein thrombosis.
- Esophagogastroscope shows esophageal varices.

Etiology
- In adults:
  - Cirrhosis (common cause)
  - Hypercoagulable states
  - Inflammatory diseases
  - Complications of medical intervention: ambulatory dialysis, chemoembolization, liver transplantation, partial hepatectomy, sclerotherapy, splenectomy, TIPS
  - Infections: appendicitis, diverticulitis, cholecystitis
- In children: umbilical sepsis

Treatment
- Variceal sclerotherapy or banding
- Surgical mesocaval or splenorenal shunt

314 PRIMARY SCLerosING CHOLANGITIS
Definition
Disorder characterized by segmental fibrosing inflammation of the intrahepatic and extrahepatic bile ducts.
Diagnosis
Labs
- ↑ Alk phos (90%); + pANCA (90%); ↑ AST, bil; + ANA
- Liver bx: obliterative cholangitis, periductal onion ring fibrosis

Imaging
- Cholangiography (ERCP, MRCP)

Etiology
- Unknown, suspected primary autoimmune disorder

Treatment
- Liver transplantation

Clinical Pearl
- Associated w/IBD

**315 PROLACTINOMA**

Definition
Monoclonal tumor that secretes prolactin. Microadenomas (<10 mm diameter) or macroadenomas (>10 mm diameter).

Diagnosis

H&P
- **Men:** ↓ facial and body hair, small testicles, ↓ libido, erectile dysfunction, and delayed puberty
- **Women:** amenorrhea, galactorrhea, oligomenorrhea, and anovulation
- **Both sexes:** visual field defects and headache, depending on size of tumor and its expansion

Labs
- ↑ Serum prolactin level. Levels >300 ng/mL are virtually dx of prolactinomas. Serial measurements are recommended in pts w/mild prolactin elevations.
- TRH stimulation test: useful in equivocal cases. The nl response is ↑ in serum prolactin levels by 100% within 1 hr of TRH infusion; failure to demonstrate ↑ in prolactin level is suggestive of pituitary lesion.

Imaging
- MRI of pituitary w/gadolinium enhancement

Treatment
- Management of prolactinomas depends on their size and encroachment on the optic chiasm and other vital structures, the presence or absence of gonadal dysfunction, and the pt’s desires w/respect to fertility.
- Medical Rx (bromocriptine, cabergoline): preferred when fertility is an important consideration.
- Transsphenoidal resection: option in infertile pts who cannot tolerate bromocriptine or cabergoline or when medical Rx is ineffective. The success rate depends on the location of the tumor (entirely intrasellar), experience of the neurosurgeon, and size of the tumor (<10 mm in diameter); the recurrence rate may reach 80% within 5 yr.
- Pituitary irradiation: useful as adjunctive Rx of macroadenomas (>10 mm in diameter) and in pts w/persistent hypersecretion after surgery.
- Stereotactic radiosurgery (gamma knife): a high dose of ionizing radiation is delivered to the tumor through multiple ports. Its advantage is min. irradiation to surrounding tissues. Proximity of the tumor to the optic chiasm limits this therapeutic modality.
- Pts receiving medical Rx require periodic measurement of prolactin levels. An attempt to ↓ the dose of bromocriptine or cabergoline can be made after the prolactin level has been nl for 2 yr. An MRI scan of the pituitary should be obtained to r/o tumor enlargement within 6 mo of initiation of tapering regimen.

Clinical Pearls
- Transsphenoidal surgery will result in a cure in nearly 50%-75% of pts w/microadenomas and 10%-20% of pts w/macroadenomas.
- Nearly 20% of microprolactinomas resolve during long-term dopamine agonist treatment.
PROSTATE CANCER

Staging
- Stage A: Confined to the prostate, no nodule palpable
- Stage B: Palpable nodule confined to the gland
- Stage C: Local extension
- Stage D: Regional lymph nodes or distant mets

In the Gleason classification, two histologic patterns are independently assigned numbers 1-5 (best to least differentiated). These numbers are added to give a total tumor score between 2 and 10. Prognosis is best for highly differentiated tumors (e.g., Gleason score 2-4) compared with most poorly differentiated tumors (Gleason score 7-10).

Another commonly used classification is the tumor-node-metastasis (TNM) classification of prostate cancer.

Diagnosis

H&P
- Generally silent disease until it reaches advanced stages. Local growth can cause sx of outflow obstruction.
- Bone pain and pathologic Fx may be initial sx of prostate cancer.
- DRE: area of ↑ firmness

Labs
- Measurement of PSA is controversial in early dx of prostate cancer. PSA screening is associated w/psychological harm, and its potential benefits remain uncertain. NI PSA is found in >20% of pts w/prostate cancer, whereas only 20% of men w/PSA levels between 4 and 10 ng/mL have prostate cancer. The American Cancer Society recommends offering the PSA test and DRE q yr to men ≥50 yr who have a life expectancy >10 yr. Earlier testing, starting at age 45 yr, is recommended for men at high risk (e.g., blacks, men w/FHx of prostate cancer). An isolated ↑ in PSA level should be confirmed several weeks later before proceeding w/further testing, including prostate bx. Screening for prostate cancer in men ≥75 yr is controversial and generally not recommended.
- Free PSA: ↑ in men w/BPH. For example, in men w/total PSA levels of 4 to 10 ng/mL, the cancer probability is 0.25; but if the percentage of free PSA is ≤17%, the probability of cancer ↑ to 0.45.
- PSA velocity: the rate of ↑ of serum PSA (PSA velocity) can aid in the dx of prostate cancer. A yearly PSA velocity >0.75 ng/mL ↑ the likelihood of later malignancy when total PSA is still within nl range. Proper interpretation of PSA velocity requires at least 3 PSA measurements during an 18-mo period because most PSA variations are physiologic.
- Age-adjusted PSA: there is evidence that the current threshold of 4.0 ng/mL is inadequate for younger men because in a study, 22% of men w/PSA levels between 2.6 and 4.0 were found to have prostate cancer. The concept of age-related cutoffs remains controversial. Lowering of the upper limit of nl for PSA would improve sensitivity but ↓ specificity.
- Transrectal bx and fine-needle aspiration of prostate can confirm the dx. Indications for bx include an abnl PSA level, an abnl DRE, or a previous bx specimen that showed prostatic intraepithelial neoplasia or prostatic atypia. The number of cores taken is pt specific, typically including a min. of 10 cores. Prostate volume negatively affects cancer detection rate (23% in glands >50 cm³, 38% in glands <50 cm³).

Imaging
- Bone scan: useful to evaluate bone metastasis; however, it is not required for staging of prostate cancer in asymptomatic men w/clinically localized cancer if the PSA level is ≤20 ng/mL.

Treatment
- Therapeutic approach varies w/the following:
  - Stage of the tumor
  - Pt’s life expectancy
  - General medical condition
  - Pt’s treatment preference (e.g., pt may be opposed to orchietomy)
Chapter 3 Diseases and Disorders

- Localized cancer
  - Radical prostatectomy: in pts w/life expectancy >10 yr
  - Radiation Rx (external beam irradiation or brachytherapy w/implantation of radioactive pellets [iodine I 125 or palladium Pd 103 seeds] into the prostate gland)
  - Watchful waiting: in pts who are too old or too ill to survive >10 yr
- Advanced disease: radiation Rx and hormonal Rx (diethylstilbestrol, LHRH analogues, antiandrogens, bilateral orchiectomy)

Clinical Pearls
- Prognosis varies w/stage of the disease and the Gleason classification. For pts between 65 and 69 yr of age at dx and a Gleason score of 2-4, the probability of dying of prostate cancer 15 yr after dx is 0.06, and that of dying of other causes is 0.56. If the Gleason score is 7-10, the probability of dying of prostate cancer ↑ up to 0.72 and of other causes varies from 0.25-0.36.
- The ploidy of the tumor also has prognostic value: prognosis is better w/diploid tumor cells, worse w/aneuploid tumor cells.
- For grade 1 tumors, the extended 10-yr, disease-specific survival is similar for pts w/prostatectomy (94%), radiotherapy (90%), and conservative management (93%); survival rate is better w/surgery than w/radiotherapy or conservative management in pts w/grade 2 or 3 localized prostate cancer.

317 PROSTATITIS

Definition
Prostatitis refers to inflammation of the prostate gland. There are four major categories:
- Acute bacterial prostatitis (type I)
- Chronic bacterial prostatitis (type II)
- Chronic prostatitis/pelvic pain syndrome (type III): subdivided into type IIIA (inflammatory) and type IIIB (noninflammatory)
- Asymptomatic inflammatory prostatitis (type IV)

Diagnosis

H&P
- Acute bacterial prostatitis: sudden or rapidly progressive onset of
  - Dysuria
  - Frequency
  - Urgency
  - Nocturia
  - Perineal pain that may radiate to the back, the rectum, or the penis
  - Hematuria or a purulent urethral d/c, urinary retention, fever, chills, and signs of sepsis can also be part of the clinical picture.
  - On rectal examination, the prostate is typically tender.
- Chronic bacterial prostatitis: characterized by + culture of expressed prostatic secretions. May cause sx such as suprapubic, low back, or perineal pain and mild urgency, frequency, and dysuria w/urination; may be associated w/recurrent UTIs.
- Chronic prostatitis/chronic pain syndrome: manifested w/pain in the pelvic region >3 mo. Sx also can include pain in the suprapubic region, low back, penis, testes, or scrotum.

Labs
- U/A, urine C&S
- Cell count and culture of expressed prostatic secretions
- CBC and blood cultures if fever, chills, or signs of sepsis exist

Etiology
- Acute bacterial prostatitis: usually gram-negative infection of the prostate gland from the ascent of bacteria in the urethra
- Chronic bacterial prostatitis: exacerbation of sx of BPH caused by the same mechanism as in acute bacterial prostatitis
- Chronic prostatitis/chronic pain syndrome:
• Type IIIA: sx of prostatic inflammation associated w/the presence of WBCs in prostatic secretions w/no identifiable bacterial organism. *Chlamydia* infection may be etiologically implicated in some cases.
• Type IIIB: refers to sx of prostatic inflammation w/no or few WBCs in the prostatic secretion. Cause is unknown. Spasm in the bladder neck or urethra may be responsible for the sx.

**Treatment**
- Acute bacterial prostatitis: ciprofloxacin 500 mg bid pending culture results; culture-guided abx Rx for 4 wk
- Chronic bacterial prostatitis
  - TMP-SMZ for 4 wk if the organism is sensitive
  - Second-line choice for treatment failure or organisms resistant to TMP-SMX is a quinolone.
- Chronic prostatitis/chronic pain syndrome
  - No specific treatment. A brief course of NSAIDs may be tried until urine localization cultures are completed.
  - Abx are not effective and should be avoided in pts who are afebrile and have nl U/A results.
  - A trial of treatment w/an α-adrenergic blocker (terazosin, doxazosin, or tamsulosin) may be considered, but trials failed to show a significant reduction in sx.

### PSEUDOGOUT (CALCIUM PYROPHOSPHATE DEHYDRATE DEPOSITION DISEASE)

**Definition**
Crystal-induced synovitis resulting from the deposition of Ca pyrophosphate dehydrate (CPPD) crystals in joint hyaline and fibrocartilage. The cartilage deposition is termed *chondrocalcinosis*.

**Diagnosis**
- American Rheumatism Association criteria:
  - I. Demonstration of CPPD crystals (obtained by bx, arthroscopy or aspirated synovial fluid) by definitive means (e.g., characteristic “fingerprint” by x-ray diffraction powder pattern or by chemical analysis)
  - IIa. Identification of monoclinic or triclinic crystals showing either no or only a weakly positive birefringence by compensated polarized light microscopy
  - IIb. Presence of typical calcifications on radiographs
  - IIIa. Acute arthritis, especially of knees or other large joints, w/ or w/o concomitant hyperuricemia
  - IIIb. Chronic arthritis, especially of knees, hips, wrists, carpus, elbow, shoulder, and metacarpophalangeal joints, especially if accompanied by acute exacerbations; the following features are helpful in differentiating chronic arthritis from osteoarthritis:
    - Uncommon site—for example, wrist, MCP, elbow, shoulder
    - Appearance of lesion radiologically—for example, radiocarpal or patellofemoral joint space narrowing, especially if isolated (patella “wrapped around” the femur)
    - Subchondral cyst formation
    - Severity of degeneration—progressive, w/subchondral bone collapse (microFxs), and fragmentation, w/formation of intra-articular radiodense bodies
    - Osteophyte formation—variable and inconstant
    - Tendon calcifications, especially Achilles, triceps, obturators
- Categories
  - Definite: criterion I or IIa plus IIb must be fulfilled.
  - Probable: criterion IIa or IIb must be fulfilled.
  - Possible: criterion IIIa or IIIb should alert the clinician to the possibility of underlying CPPD deposition.

**Treatment**
- NSAIDs (as for gout)
- Colchicine
- Aspiration/steroid injection
319 PSEUDOMEMBRANOUS COLITIS

Definition
Occurrence of diarrhea and bowel inflammation associated w/abx use.

Diagnosis
H&P
- Diarrhea, fever, and abd cramps after use of abx
Labs
- ELISA for C. difficile toxins A and B
- CBC: leukocytosis. A sudden ↑ in WBC to >30,000/mm³ may be indicative of fulminant colitis.

Etiology
- Cephs are the most frequent offending agent because of their ↑ rates of use.
- Abx w/the highest incidence is clindamycin (10% incidence of pseudomembranous colitis w/its use).

Treatment
- Discontinue offending abx.
- Fluid hydration and correction of electrolyte abnormalities
- Metronidazole 250 mg PO qid × 10-14 days
- Vancomycin 125 mg PO qid × 10-14 days in cases resistant to metronidazole
- Cholestyramine 4 g PO qid × 10 days in addition to metronidazole for severe diarrhea (avoid use w/vancomycin)
- When parenteral Rx is necessary (e.g., pt w/paralytic ileus), IV metronidazole 500 mg qid can be used. It can also be supplemented w/vancomycin 500 mg by NG tube or enema.
- IV tigecycline can be used as adjunctive or alternative Rx for severe refractory C. difficile infection (Clin Inf Dis 48:1732, 2009).

320 PULMONARY EDEMA, CARDIOGENIC

Definition
Life-threatening condition caused by severe LV decompensation.

Diagnosis
H&P
- Dyspnea w/rapid, shallow breathing
- Diaphoresis, perioral and peripheral cyanosis
- Pink, frothy sputum
- Moist, bilateral pulmonary rales
- ↑ Pulmonary second sound, S₃ gallop (in association w/tachycardia)
- Bulging neck veins
Labs
- ABGs: respiratory and metabolic acidosis, ↓ PaO₂, ↑ P CO₂, ↓ pH. (NOTE: the pt may initially show respiratory alkalosis secondary to hyperventilation in attempts to maintain PaO₂.)
- ↑ BNP
Imaging
- CXR: pulmonary congestion w/Kerley B lines; fluffy perihilar infiltrates in the early stages; bilateral interstitial alveolar infiltrates, pleural effusions in later stages
- Echo: useful to evaluate valvular abnormalities, diastolic vs. systolic dysfunction
- Right-sided heart catheterization (selected pts): cardiac pressures and cardiogenic pulmonary edema reveal ↑ PADP and PCWP ≥25 mm Hg

Etiology
- Acute MI
- Exacerbation of CHF
- Valvular regurgitation
- VSD
- Severe myocardial ischemia
- Mitral stenosis
- Other: cardiac tamponade, endocarditis, myocarditis, arrhythmias, cardiomyopathy, HTN crisis
**Treatment**

All the following steps can be performed concomitantly:

- **Supplemental O₂:** 100% oxygen by face mask, CPAP, BiPAP, NIPPV; intubate if marked hypoxemia or severe respiratory acidosis
- **Furosemide:** 1 mg/kg IV bolus (typically 40-100 mg); may double the dose in 30 min if no effect
- **Vasodilator Rx:**
  - Nitrates: NTG: 150-600 µg SL, 2% NTG ointment (1-3 inches; absorption may be erratic), IV NTG (100 mg in 500 mL of D₂W solution; start at 6 µg/min [2 mL/hr])
  - Nitroprusside: for afterload reduction in hypertensive pts w/ ∆ Cl
  - Vasodilator and diuretic Rx should be tailored to achieve PCWP ≤18 mm Hg, RAP ≤8 mm Hg, systolic BP >90 mm Hg, SVR >1200 dyn-sec/cm⁻5.
  - Nesiritide: reserved only for selected pts resistant to combination Rx w/diuretics and NTG. Dosage is 2 µg/kg IV bolus, then 0.01 µg/kg/min.
- **Morphine:** 2-4 mg IV, SC, or IM; may repeat q15min PRN. It may induce hypotension in volume-depleted pts.
- **Afterload reduction w/ACEIs.** Captopril 25 mg PO tablet can be used for SL administration (placing a drop or two of water on the tablet and placing it under the tongue helps dissolve it); onset of action is <10 min, peak effect can be reached in 30 min. ACEIs can also be given IV (e.g., enalaprilat 1 mg IV given q2h PRN).
- **Dobutamine:** parenteral inotropic agent of choice in severe cases of cardiogenic pulmonary edema. It can be administered at a dosage of 2.5-10 µg/kg/min IV. IV phosphodiesterase inhibitors (amrinone, milrinone) may be useful in refractory cases.

**Clinical Pearl**

- Acute cardiogenic pulmonary edema caused by HOCM can be treated w/IV NS solution and negative inotropic agents such as verapamil and β-blockers.

<table>
<thead>
<tr>
<th>321</th>
<th>PULMONARY EMBOLISM (PE)</th>
</tr>
</thead>
</table>

**Definition**

Lodging of a thrombus or other embolic material from a distant site in the pulmonary circulation.

**Diagnosis** (Box 3-10, Figs. 3-41 and 3-42)

- Most common sx: dyspnea
- Chest pain: may be nonpleuritic or pleuritic (infarction)
- Syncope (massive PE)

**FIGURE 3-41.** Diagnostic algorithm for suspected PE in a patient without hypotension or shock. This assessment of clinical probability is based on the Wells score (which has a range of 0-12.5, with higher scores indicating higher clinical probability). The revised Geneva score may be used as an alternative. If a moderately sensitive latex-derived D-dimer assay is used instead of the highly sensitive enzyme-linked immunosorbent D-dimer assay, PE can be ruled out only in patients with a low clinical probability. Alternatively, the Wells score can be dichotomized, classifying PE as unlikely (≤4.0) or likely (>4.0). For patients in whom PE is considered unlikely, either a highly sensitive or a moderately sensitive D-dimer assay can be used to rule out the diagnosis without need for further testing. If multidetector CT pulmonary angiography, with or without venography, is normal in a patient with a high clinical probability, the possibility of a false-negative result should be considered and further testing performed to rule out PE. Options include serial venous ultrasonography, ventilation-perfusion lung scanning, and pulmonary angiography. If a multidetector CT scan shows only subsegmental defects in a patient with a low clinical probability, the possibility of a false-positive result should be considered, and further testing (e.g., venous ultrasonography) should be performed to confirm the diagnosis. This may also apply to patients with an intermediate clinical probability, although the need for further tests is less well established for these patients.
**Box 3-10 • Probability Assessment Methods for Pulmonary Embolism**

Wells et al. have developed the following clinical prediction rules to determine the probability of PE, assigning a score to each finding:

- Clinical signs/sx of DVT (minimum of leg swelling and pain w/palpation of the deep veins of the legs) (score = 3.0)
- No alternative dx likely or more likely than PE (score = 3.0)
- HR >100 bpm (score = 1.5)
- Immobilization or surgery in last 4 wk (score = 1.5)
- Previous h/o DVT or PE (score = 1.5)
- Hemoptysis (score = 1.0)
- Cancer actively treated within last 6 mo (score = 1.0)

Probability of PE is high if total score is >6; moderate if 2-6; and low if <2.

Le Gal et al. have developed another clinical prediction rule that does not require subjective diagnostic judgments or tests. The score consists of 8 variables:

- Age >65 yr (1 point)
- Previous DVT or PE (3 points)
- Surgery of Fx within 1 mo (2 points)
- Active malignant condition (2 points)
- Unilateral lower limb pain (3 points)
- Hemoptysis (2 points)
- HR 75-94 bpm (3 points)
- HR ≥95 bpm (5 points)
- Pain on lower deep venous palpation and unilateral edema (4 points)

Probability of PE: 8% (low probability) in pts w/0-3 points; 28% (intermediate probability) with 4-10 points; 74% (high probability) with ≥11 points.

---

**Clinical probability score**

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms and signs of DVT</td>
<td>3.0</td>
</tr>
<tr>
<td>HR &gt; 100 bpm</td>
<td>1.5</td>
</tr>
<tr>
<td>Recent immobilization or surgery (≤4wk)</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.0</td>
</tr>
<tr>
<td>PE more likely than alternative diagnosis</td>
<td>3.0</td>
</tr>
</tbody>
</table>

- Low score (<2.0) or intermediate score (2.0–6.0)
  - D-dimer assay (highly sensitive)
    - Positive: Multidetector CT
      - High score (>6.0)
      - PE confirmed: Treat
      - Low score (<2.0) or intermediate score (2.0–6.0): Negative: Do not treat
    - Negative: No PE
  - Negative: No PE
  - Low score (<2.0) or intermediate score (2.0–6.0): Negative: Do not treat

---


Fever, diaphoresis, apprehension
- Hemoptysis, cough
- Evidence of DVT may be present (e.g., swelling and tenderness of extremities)
- Cardiac exam: tachycardia, ↑ pulmonic component of S₂, murmur of tricuspid insufficiency, RV heave, right-sided S₃
- Pulmonary exam: rales, localized wheezing, friction rub
- Most common physical finding: tachypnea

**Labs**
- ABGs: ↓ PaO₂ and PaCO₂, ↑ pH
- A-a oxygen gradient (measure of the difference in oxygen concentration between alveoli and arterial blood): a nl A-a gradient makes the dx of PE unlikely.
- Plasma D-dimer by ELISA: a nl plasma D-dimer level is useful to r/o PE in pts w/non-diagnostic lung scan and a low pretest probability of PE. However, it cannot “rule in” PE because it is ↑ w/many other disorders (e.g., metastatic cancer, trauma, sepsis, postoperative state).

**Imaging**
- ECG: abnl in 85% of pts w/acute PE. Frequent abnormalities are sinus tachycardia; S₁, Q₃, T₃ pattern (10% of pts); S₁, S₂, S₃ pattern; T wave inversion in V₁ to V₆; acute RBBB; new-onset AF; ST-segment depression in lead II; RV strain.
- CXR: elevated diaphragm, pleural effusion, dilation of pulmonary artery, infiltrate or consolidation, abrupt vessel cutoff, or atelectasis. A wedge-shaped consolidation in the middle and lower lobes is suggestive of a pulmonary infarction and is known as *Hampton’s hump.*
Diseases

Although

Chapter 3 Diseases and Disorders

Spiral CT: excellent modality for dx PE. It can also detect other pulmonary disease that can mimic PE.

Lung scan (in pt w/nl CXR):
  • A nl lung scan does r/o PE.
  • A ventilation-perfusion mismatch is suggestive of PE, and a lung scan interpretation of high probability is confirmatory.

Angiography: pulmonary angiography is the gold standard; however, it is invasive, expensive, and not readily available in some clinical settings. False-positive pulmonary angiograms may result from mediastinal disorders such as radiation fibrosis and tumors.

CTA is an accurate, noninvasive tool in the dx of PE at the main, lobar, and segmental pulmonary artery levels. A major advantage of CTA over standard pulmonary angiography is its ability to dx intrathoracic disease other than PE that may account for the pt’s clinical picture. It is also less invasive, less costly, and more widely available. Its major shortcoming is its poor sensitivity for subsegmental emboli.

Gadolinium-enhanced MRA of the pulmonary arteries has a moderate sensitivity and high specificity for the dx of PE; MRA is best reserved for selected pts when CT scan and lung scan are inconclusive and the risk of pulmonary angiography is high.

Risk Stratification

Table 3-35.

Etiology

Thrombus, fat, or other foreign material

Risk factors for PE:
  • Prolonged immobilization, ↓ mobility
  • Postoperative state, major surgery

### TABLE 3-35 Stratification of Risk of Death Associated with Pulmonary Embolism and Severity-Adjusted Treatment

<table>
<thead>
<tr>
<th>Early Risk of Death</th>
<th>Shock or Hypotension (on Clinical Examination)</th>
<th>Right Ventricular Dysfunction (on Echocardiography or Multidetector CT)</th>
<th>Myocardial Injury (on Cardiac Troponin Testing)</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Present</td>
<td>Present*</td>
<td>NA¹</td>
<td>Unfractionated heparin plus thrombolysis or embolectomy</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Low-molecular-weight heparin</td>
</tr>
<tr>
<td>Non-high intermediate¹</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
<td>Low-molecular-weight heparin or fondaparinux; consider outpatient treatment</td>
</tr>
<tr>
<td>Low</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Low-molecular-weight heparin or fondaparinux; consider outpatient treatment</td>
</tr>
</tbody>
</table>

¹If RV function is normal on echocardiography or if a CT scan shows no RV dilation in a patient with hemodynamic compromise and clinically suspected pulmonary embolism, an alternative diagnosis should be sought.

¹Troponin test results do not influence risk assessment of treatment in hemodynamically compromised patients with acute pulmonary embolism.

Although it has been suggested that normotensive patients with both RV dysfunction and myocardial injury have a higher risk of death than do those with only one of these risk factors, there is currently no definitive proof that they should receive more aggressive treatment.
- Trauma to lower extremities, immobilizer or cast
- Estrogen-containing birth control pills, hormone replacement Rx
- Prior h/o DVT or PE
- CHF
- Pregnancy and early puerperium
- Visceral cancer (lung, pancreas, alimentary and GU tracts)
- Spinal cord injury
- Advanced age
- Obesity, smoking
- Hematologic disease (e.g., factor V Leiden mutation, antithrombin III deficiency, protein C deficiency, protein S deficiency, lupus anticoagulant, PV, dysfibrinogenemia, PNH, acquired protein C resistance w/o factor V Leiden, G20210A prothrombin mutation)
- COPD, DM, acute medical illness
- Prolonged air travel
- Central venous catheterization

Treatment
- Table 3-36 describes anticoagulant Rx for PE.
- Acute pulmonary artery embolectomy may be indicated in a pt w/massive pulmonary emboli and refractory hypotension.

Clinical Pearl
- The duration of oral anticoagulant treatment is 6 mo in pts w/reversible risk factors and indefinitely in pts w/persistence of risk factors that caused the initial PE.

322 PULMONARY HYPERTENSION (PPH)

Definition
Mean PAP >25 mm Hg at rest or >30 mm Hg w/exercise. Sustained ↑ in PAP due to ↑ pulmonary venous pressure, hypoxic pulmonary vasoconstriction, or ↑ flow is referred to as secondary pulmonary HTN.

Diagnosis

H&P
- Exertional dyspnea: most common presenting sx (60%)
- Fatigue and weakness
- Syncope, classically exertion related or after a warm shower w/peripheral vasodilation
- Chest pain
- Hoarse voice due to compression of recurrent laryngeal nerve by an enlarged pulmonary artery (Ortner’s syndrome)
- Loud P₂ component of the second heart sound and paradoxical splitting of second heart sound
- Right-sided S₃
- JVD
- Abd distention/ascites
- Prominent parasternal (RV) impulse
- Holosystolic TR murmur heard best along the left fourth parasternal line that ↑ in intensity w/inspiration
- Peripheral edema

Labs
- CBC: nl or may show secondary polycythemia
- ANA (r/o connective tissue disease), HIV, LFTs, antiphospholipid Abs
- ABGs: ↓ Po₂ and oxygen saturation
- PFTs: r/o obstructive or restrictive lung disease
- Overnight sleep study: r/o sleep apnea/hypopnea

Imaging
- ECG: RA enlargement (tall P wave >2.5 mV in leads II, III, aVF) and RV enlargement (RAD >100 and R wave > S wave in lead V₁)
- CXR: enlargement of the main and hilar pulmonary arteries w/rapid tapering of the distal vessels, described as peripheral oligemia. RV enlargement may be evident on lateral films.
- Spiral CT or V/Q scan: r/o PE
### TABLE 3-36  Anticoagulant Drugs for Initial Treatment of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin (IV infusion)*</td>
<td>80 IU/kg of BW as an IV bolus, followed by continuous infusion at the rate of 18 IU/kg/hr</td>
<td>Adjust infusion rate to maintain APTT between 1.5 and 2.5 times control, corresponding to therapeutic heparin levels (0.3-0.7 IU/mL by factor Xa inhibition)! Monitor platelet count at baseline and every other day from day 4 to day 14 or until heparin is stopped. Investigate for HIT if platelet count falls by ≥50% or a thrombotic event occurs.</td>
</tr>
<tr>
<td>Low-molecular-weight heparins (SC injection)!</td>
<td>Low-molecular-weight heparins have not been tested in pts w/arterial hypotension or shock and thus are not recommended for such pts. Monitoring of anti–factor Xa levels may be helpful in pts at ↑ risk for bleeding, particularly those w/moderate or severe renal involvement; the need for monitoring of anti–factor Xa levels in pregnant women remains controversial. Monitor platelet count at baseline and every 2-4 days from day 4 to day 14 or until heparin is stopped.</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1.0 mg/kg q12h or 1.5 mg/kg once qd†</td>
<td>If CrCl is &lt;30 mL/min, reduce enoxaparin dose to 1 mg/kg once qd; consider unfractionated heparin infusion as an alternative.</td>
</tr>
<tr>
<td>Tinzaparin/Fondaparinux</td>
<td>175 U/kg once qd or 5 mg (BW&lt;50 kg); 7.5 mg (BW 50-100 kg); or 10 mg (BW &gt;100 kg) administered once qd</td>
<td>This drug is contraindicated in pts w/severe renal impairment (CrCl &lt;30 mL/min). No routine platelet monitoring is necessary.</td>
</tr>
</tbody>
</table>

*Unfractionated heparin is the preferred treatment in pts w/severe renal dysfunction (CrCl <30 mL/min) because it is not eliminated by the kidneys and in pts w/↑ risk of bleeding (i.e., those w/congenital or acquired bleeding diathesis; active ulcerative or angiodysplastic GI disease; recent hemorrhagic stroke; recent brain, spinal, or ophthalmologic surgery; diabetic retinopathy; bacterial endocarditis) because of its short half-life and reversible anticoagulant effects.

†It is recommended that the treatment dose be adjusted on the basis of standardized nomograms.

‡Tinzaparin and fondaparinux are explicitly approved for the treatment of acute PE. Enoxaparin is approved for the treatment of DVT w/o or w/PE.

§This recommendation applies to postoperative pts and to medical or obstetric pts who have received unfractionated heparin within the past 100 days. For medical and obstetric pts who have received only low-molecular-weight heparin, some authorities recommend no routine monitoring of platelet counts.

¶Once-daily injection of enoxaparin at a dose of 1.5 mg/kg is approved for inpatient treatment of PE in the U.S. and in some but not all European countries. APTT, activated partial thromboplastin time.

- Doppler echo: assesses ventricular function, excludes significant valvular disease, and visualizes abnl shunting of blood between heart chambers if present. It also provides an estimate of the pulmonary artery systolic pressure.

**Etiology**

- The etiology of PPH is unknown. Most cases are sporadic, but there is a 6%-12% familial incidence. Familial PPH is an autosomal dominant disease w/variable penetrance, affecting only about 10%-20% of carriers.

- PPH is associated w/several known risk factors: portal HTN and liver cirrhosis; appetite-suppressant drugs (fenfluramine); sickle cell, hemoglobinopathies, and HIV disease.
**Treatment**

**Acute Rx**
- Diuretics (e.g., furosemide 40-80 mg qd)
- Digoxin in pts w/AF
- Short-acting vasodilators: IV adenosine, epoprostenol, or inhaled nitric oxide

**Chronic Rx**
- CCB (diltiazem, amlodipine, or nifedipine). Verapamil is not recommended because of its negative inotropic effects.
- Nonresponders are eligible for selective pulmonary vasodilators.
- Prostanoids (epoprostenol, treprostinil, and iloprost) act as potent vasodilators of pulmonary arteries and inhibitors of platelet aggregation.
- Endothelin receptor antagonists: bosentan, ambrisentan, and sitaxsentan.
- Phosphodiesterase inhibitors: sildenafil and tadalafil.
- Warfarin therapy w/goal INR 1.5-2.0 is recommended for all pts w/PPH and although not proven may be indicated in secondary pulmonary hypertension.
- Lung transplantation and heart-lung transplantation are other options in pts w/end-stage class IV disease. Atrial septostomy may be performed as a bridge to transplantation. Recommended for individuals w/a room air $\text{SaO}_2 > 90\%$ who suffer from severe right-sided heart failure (w/refractory ascites) despite max diuretic Rx or who have signs of impaired systemic blood flow (such as syncope) due to ↓ left-sided heart filling.

**PULSELESS ELECTRICAL ACTIVITY (PEA, ELECTROMECHANICAL DISSOCIATION)**

**Definition**
Absence of CO in the presence of organized electrical activity.

**Diagnosis**

**Primary PEA**
- Organized electrical activity (not VT/VF)
- No detectable pulse

**Secondary PEA**
- Bradycardia: drug OD
- Tachycardia: hypovolemia, massive PE
- ↓ JVP: hypovolemia
- ↑ JVP and no pulse w/CPR: cardiac tamponade, massive PE, tension pneumothorax
- Absent unilateral breath sounds w/mechanical ventilation and tracheal deviation: tension pneumothorax
- Cyanosis: hypoxia

**Labs**
- CBC
- Lytes, BUN, Cr, Mg, Ca
- ABGs

**Imaging**
- ECG (Fig. 3-43)
  - Low voltage: tamponade
  - Right-sided heart strain: PE, pneumothorax
  - Arrhythmias: MI, metabolic abnormalities, drug effects
  - ST changes, Q waves: MI
- CXR: r/o pneumothorax

**Figure 3-43.** Sinus rhythm with pulseless electrical activity. Although the ECG showed sinus rhythm, the patient had no pulse or BP. In this case, the PEA was a result of depressed myocardial function after a cardiac arrest.
Pyelonephritis

**Definition**
Infection, usually bacterial in origin, of the upper urinary tract.

**Diagnosis**

**H&P**
- Fever, flank pain, dysuria, hematuria

**Labs**
- CBC w/diff, blood cultures, U/A, urine C&S, BUN, Cr, Gram stain of urine

**Imaging**
- Renal U/S: if obstruction or closed space infection suspected
- CT scan: suspected abscess, calculi
Etiology
- Gram-negative bacilli: *E. coli* and *Klebsiella* spp in >95% of cases
- Resistant gram-negative organisms or fungi: hospitalized pts w/indwelling catheters
- Gram-positive organisms: *Staphylococcus aureus*: hematogenous spread

Treatment
- Stable pt w/sensitive pathogens: ciprofloxacin (500 mg bid × 10 days)
- Severe/complicated infection: ampicillin 1-2 g IV q4-6h + AGs; alternative regimen: ceftazidime 2 g IV q8h or piperacillin 3 g IV q6h
- Prompt drainage w/nephrostomy tube placement for obstruction
- Surgical drainage of large collections of pus

**325 RAMSAY HUNT SYNDROME**

Definition
Localized herpes zoster infection involving the seventh nerve and geniculate ganglia, resulting in hearing loss, vertigo, and facial nerve palsy.

Diagnosis
- Facial paralysis on the involved side
- Characteristic vesicles: on pinna, in external auditory canal in distribution of the facial nerve and, occasionally, adjacent cranial nerves

Etiology
- Reactivation of dormant infection w/varicella-zoster virus after primary varicella

Treatment
- Prednisone 60 mg on day 1, ↓ by 10 mg/day until finished
- Acyclovir (800 mg PO 5x qd × 10 days), famciclovir (500 mg tid × 7 days), or valacyclovir (1 g q8h × 7 days)

**326 RAYNAUD’S PHENOMENON (RP)**

Definition
Vasospastic disorder that produces an exaggerated response to cold temperatures or emotional stress, resulting in transient digital ischemia.

Diagnosis

**H&P**
- It classically is manifested in 3 stages:
  - Pallor phase: the initial spasm causes ↓ cutaneous blood flow, resulting in pallor, numbness, paresthesias, and pain in the affected digits.
  - Cutaneous cyanosis: the digits develop a blue-purple color caused by deoxygenated blood in the capillary bed.
  - Hyperemic phase: ↑ blood flow to the affected digits resulting from the reopening of the digital artery results in blushing of the skin.
- RP is classified clinically into primary or secondary forms and affects approximately 3% of the general population.
  - Primary RP usually occurs between the ages of 15-25 yr. It is more likely to affect women than men and appears to be more common in colder climates.
  - Secondary RP tends to begin after 35-40 yr of age.
  - Secondary RP occurs in more than 90% of pts w/scleroderma and in about 30% of pts w/SLE and SS.
  - There is also some suggestion that secondary RP may be associated w/drugs (nicotine, caffeine, ergotamine, vinyl chloride) or trauma to the hands from vibrating tools such as jack hammers.

Labs
- ANA
- If the hx, PE, and initial laboratory tests suggest a possible secondary cause, specific serologic testing (e.g., anticentromere Abs, anti-Scl-70, cryoglobulins, complement testing, and protein electrophoresis) may be indicated.
Noninvasive vascular testing includes finger systolic BPs, segmental BP measurements, cold recovery time (measure vasoconstrictor and vasodilator responses of finger to cold), fingertip thermography, and laser Doppler w/thermal challenge (measure relative change in skin blood flow w/ambient warming).

**Treatment**
- Avoid triggering factors (cold ambient temperatures, emotional stress, drugs [tobacco, caffeine, antihistamines, amphetamines, cocaine, β-blockers, estrogen replacement]).
- CCBs are the most effective treatment.
- α-Receptor blockers (prazosin or doxazosin)
- Other vasodilator drugs alone or in combination: NTG, hydralazine, papaverine, minoxidil, niacin, and topical nitrates
- Anticoagulation w/ASA and heparin during the acute phase of an ischemic event. Long-term anticoagulation w/heparin or warfarin is not recommended unless there is evidence of a hypercoagulable disorder.
- Bypass surgery: for severe RP associated w/reconstructable arterial occlusive disease
- Sympathectomy: for unreconstructable occlusive disease or pure vasospastic disease refractory to medical treatment

**REITER’S SYNDROME AND REACTIVE ARTHRITIS**

**Definition**
- Reiter’s syndrome is one of the “seronegative spondyloarthropathies” (so called because serum RF is not present in these forms of inflammatory arthritis). There is an international consensus that the term reactive arthritis replace the name Reiter’s syndrome to describe this constellation of signs and sx. Reactive arthritis (ReA) represents two syndromes: Reiter’s syndrome, occurring after nongonococcal urethritis, and the other following infectious diarrhea, most often caused by campylobacter.
- Reiter’s syndrome is an asymmetric polyarthritis that affects mainly the LEs and is associated w/one or more of the following:
  - Urethritis
  - Cervicitis
  - Dysentry
  - Inflammatory eye disease
  - Mucocutaneous lesions

**Diagnosis**

**Clinical Presentation**
- Polyarthritis: affecting the knee and ankle, commonly asymmetric
- Heel pain and Achilles tendinitis, especially at the insertion of the Achilles tendon
- Plantar fasciitis
- Large effusions
- Dactylitis or “sausage toe”
- Urethritis
- Uveitis or conjunctivitis; uveitis can progress to blindness w/o treatment
- Keratoderma blennorrhagicum, circinate balanitis: hyperkeratotic lesions on soles of the feet, toes, penis, hands; closely resembles psoriasis
- Aortic regurgitation similar to that seen in ankylosing spondylitis

**Labs**
- HIV testing is recommended, especially if risk factors such as unprotected sexual activity and IV drug use are identified.
- No specific lab test to dx Reiter’s syndrome

**Imaging**
- Plain radiographs:
  - Juxta-articular osteopenia of affected joints
  - Erosions and joint space narrowing in more advanced disease
  - Periostitis and reactive new bone formation at the insertions of the Achilles tendon and the plantar fascia
Sacroiliitis: unilateral or bilateral
Indistinguishable from ankylosing spondylitis
Vertebral bridging osteophytes

Etiology
- Epidemic reactive arthritis after outbreaks of dysentery has been described.
- Genetically susceptible HLA-B27 individuals are at risk for development of ReA after infection with certain pathogens: Salmonella, Shigella, Yersinia enterocolitica, Chlamydia trachomatis.
- Symptom complex indistinguishable from Reiter’s syndrome has also been described in association with HIV infection.

Treatment
- Enteric or urethral infection: appropriate abx coverage
- Uveitis: steroid eye drops in consultation with an ophthalmologist
- Achilles tendinitis and plantar fasciitis: NSAIDs and injections of methylprednisolone (40-80 mg)
- Sulfasalazine (2-3 g PO tid) may be effective.
- Flares can be treated with NSAIDs. Persistent and uncontrolled disease should be managed with cytotoxic drugs (MTX, azathioprine) in consultation with a rheumatologist.

Clinical Pearl
- Infection with HIV is associated with particularly severe cases of Reiter’s syndrome.

328 RENAL ARTERY STENOSIS (RAS)

Diagnosis

H&P
- Acute renal artery occlusion
  - Flank or abd pain
  - Fever
  - N/V
  - Leukocytosis
  - Hematuria (microscopic or gross)
  - AST, LDH, and alk phos
  - Oliguric renal failure if occlusion is bilateral; nl or nearly nl renal function in unilateral occlusion
- Cholesterol emboli: multisystem manifestations resembling vasculitis (visual disturbance, painful distal extremities, abd pain, signs of organ or limb ischemia). Lab findings include eosinophiluria, proteinuria, renal failure, ↑ ESR.
- Progressive RAS
  - HTN in a young pt w/o FHx of such (fibromuscular dysplasia), new-onset HTN at age <30 yr or >55 yr, uncontrolled HTN refractory to >3 meds, HTN pt w/o FHx or risk factors
  - HTN in a middle-aged man w/other evidence of atheromatous disease
  - Abd bruit (40% of cases)
  - Renal failure
  - Hypertensive retinopathy
  - Pulmonary edema in a hypertensive pt
  - Hypokalemia
  - Renal failure after the administration of ACEI (if bilateral RAS)

Labs
- Cr, K+, U/A
- Peripheral PRA
- Captopril test (stimulation of excessive renin secretion)

Imaging
- MRA: test of choice
- CTA: fast and effective but requires infusion of iodinated contrast material
- Duplex U/S: safe and inexpensive, but highly operator dependent and poor evaluation of accessory renal arteries
- Digital subtraction angiography (88% sensitivity and 90% specificity)
**Etiology**

*Renal Artery Thrombosis*
- Atherosclerosis
- Fibromuscular dysplasia: classified into 3 categories by the layer of arterial wall affected (intimal, medial, adventitial)
- Arteritis
- Aneurysm
- Arteriography
- Syphilis
- Hypercoagulable state
- Complication of renal transplantation (role of cyclosporine)

*Renal Artery Embolism (cardiac conditions [90%])*
- MI
- AF
- Cardiomyopathy
- Endocarditis
- Paradoxical emboli from DVT in pt w/cardiac septal defect
- Atheromatous plaques (cholesterol emboli)

**Treatment**
- Acute renal artery thrombosis or embolism
  - Thrombolytic Rx
  - Anticoagulation
  - Revascularization (surgery)
  - BP control
- Cholesterol emboli: statins
- RAS
  - BP control. Role of ACEIs and ARBs is controversial; both directly counter the activation of the renin-angiotensin system and are ideal agents, but neither should be continued if renal function worsens. They should be avoided in bilateral renal stenosis or unilateral stenosis w/solitary kidney.
  - Angioplasty or revascularization should be reserved for pts whose BP control w/medication is difficult and for pts w/progressive renal failure.

**Clinical Pearls**
- RAS caused by fibromuscular dysplasia generally does not progress.
- RAS associated w/atherosclerosis is progressive. Of pts w/>60% stenosis, 5% progress to total occlusion in 1 yr and 11% progress in 2 yr.

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**RENAL FAILURE, ACUTE**

*Marc S. Weinberg*

**Definition**
Acute renal failure (ARF) is the rapid impairment in renal function resulting in retention of products in the blood that are normally excreted by the kidneys.

**Diagnosis**

*Physical Findings and Clinical Presentation*
PE should focus on volume status. The physical findings noted here vary w/the duration and rapidity of onset of renal failure:
- Peripheral edema
- Skin pallor, ecchymoses
- Oliguria (however, pts can have nonoliguric renal failure), anuria
- Fasciculations change in diurnal sleep patterns; daily fatigue and nocturnal insomnia
- Tachypnea, tachycardia
- Weakness, anorexia, generalized malaise, nausea

**Labs** *(Tables 3-37 and 3-38)*
- Serum Cr: the rate of rise of Cr is approximately 1 mg/dL/day in complete renal failure or 2 mg/dL/day in obstruction.
- BUN: BUN/Cr ratio >20:1 in prerenal azotemia, postrenal azotemia, and AGN; <20:1 in AIN and ATN
- Electrolytes: ↑ K⁺, PO₄ and ↓ HCO₃, Ca
DISEASES AND DISORDERS

**Chapter 3**

**TABLE 3-37** Serum and Radiographic Abnormalities in Renal Failure

<table>
<thead>
<tr>
<th></th>
<th>Prerenal</th>
<th>Postrenal (Acute)</th>
<th>Intrinsic Renal (Acute)</th>
<th>Intrinsic Renal (Chronic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN</td>
<td>↑ 10:1 &gt; Cr</td>
<td>↑ 20-40/day</td>
<td>↑ 20-40/day</td>
<td>Stable, ↑ varies w/protein intake</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>NL/moderate ↑</td>
<td>↑ 2-4/day</td>
<td>↑ 2-4/day</td>
<td>Stable ↑ (production = excretion)</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>NL/moderate ↑</td>
<td>↑ varies w/urinary volume</td>
<td>↑↑ (particularly when pt is oliguric) ↑↑↑ w/rhabdomyolysis</td>
<td>NL until end stage, unless tubular dysfunction (type 4 renal tubular acidosis)</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>NL/moderate ↑</td>
<td>Moderate ↑ ↑↑ w/rhabdomyolysis</td>
<td>↑ Poor correlation w/duration of renal disease</td>
<td>Becomes significantly ↑ when serum Cr surpasses 3 mg/dL</td>
</tr>
<tr>
<td>Serum Ca</td>
<td>NI</td>
<td>NI/↓ w/ P04− retention</td>
<td>↓ (poor correlation w/duration of renal failure)</td>
<td>Usually ↓</td>
</tr>
<tr>
<td>Renal size by U/S</td>
<td>NI/↑</td>
<td>↑ and dilated calyces</td>
<td>NI/↑</td>
<td>↓ and w/↑ echogenicity</td>
</tr>
<tr>
<td>FENa*</td>
<td>&lt;1</td>
<td>&lt;1 → &gt;1</td>
<td>&gt;1†</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>

*FENa* = \[ \frac{\text{U/P Na}− × 100}{\text{U/P Cr}} \] (useful only in oliguric pt).

†May be ≤ 1 in radiocontrast-induced myoglobinuric acute tubular necrosis and in early sepsis.

**TABLE 3-38** Urinary Abnormalities in Renal Failure

<table>
<thead>
<tr>
<th></th>
<th>Prerenal</th>
<th>Postrenal (Acute)</th>
<th>Intrinsic Renal (Acute)</th>
<th>Intrinsic Renal (Chronic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary volume</td>
<td>↓</td>
<td>Absent to wide fluctuation</td>
<td>Oliguric or nonoliguric</td>
<td>≥100 mL + until end stage</td>
</tr>
<tr>
<td>Urinary Cr</td>
<td>↑ (U/P Cr ± 40)</td>
<td>↓ (U/P Cr ± 20)</td>
<td>↓ (U/P Cr &lt;20)</td>
<td>↓ (U/P Cr &lt;20)</td>
</tr>
<tr>
<td>Osmolarity</td>
<td>↑ (±400 mOsm/kg)</td>
<td>&lt;350 mOsm/kg</td>
<td>&lt;350 mOsm/kg</td>
<td>&lt;350 mOsm/kg</td>
</tr>
<tr>
<td>Degree of proteinuria</td>
<td>Minimum</td>
<td>Absent</td>
<td>Varies w/cause of renal failure</td>
<td>Varies w/cause of renal disease (from 1-2 g/day to nephrotic range)</td>
</tr>
</tbody>
</table>

**Urinary sediment**

Negative, or occasionally hyaline cast

Negative or hematuria w/stones or papillary necrosis

Pyuria w/infectious prostatic disease

ATN: muddy brown casts

Interstitial nephritis: lymphocytes, eosinophils (in stained preparations), and WBC casts

RPGN: RBC casts

Nephrosis: oval fat bodies

Broad casts w/variable renal “residual” acute findings

*Except NSAID-induced allergic interstitial nephritis w/concomitant “nil disease.”

Clearance = (urinary concentration × urinary volume) ÷ plasma concentration; U/P, urine/plasma ratio.
Chapter 3  Diseases and Disorders

- CBC: anemia (due to ↓ erythropoietin production, hemoconcentration, or hemolysis)
- U/A: RBC, WBC, casts, smoky color in the presence of intrinsic renal disease
- Hematuria and pyuria are seen in many intrinsic diseases; eosinophiluria (AIN); RBC casts in GN; WBC casts in AIN; muddy brown casts w/ATN; proteinuria (nephrotic syndrome)
- Urinary sodium and urinary Cr should also be obtained to calculate the $\text{FE}_{\text{Na}}$ ($\text{FE}_{\text{Na}} = \text{urine Na}/\text{plasma Na} \times \text{plasma Cr}/\text{urine Cr} \times 100$). The $\text{FE}_{\text{Na}}$ is <1 in prerenal failure, >1 in intrinsic renal failure in pts w/urine output <400 mL/day w/the exception of low-flow states such as low tubular flow states, diseases w/marked reductions in intravascular volume, and contrast nephropathy.
- Urinary osmolarity: 250-300 mOsm/kg in ATN, <400 mOsm/kg in postrenal azotemia, and >500 mOsm/kg in prerenal azotemia and AGN
- Additional useful studies are electrolytes, Ca, P, Hgb, blood cultures for pts suspected of sepsis, LFTs, immunoglobulins, protein IEP in pts suspected of myeloma, uric acid, complements and ANA for vasculitis and connective tissue diseases, review of the peripheral blood smear

**Imaging**
- CXR: evaluate for CHF and for pulmonary renal syndromes (Goodpasture’s syndrome, Wegener’s granulomatosis).
- KUB: may demonstrate kidney size and shape; calcifications may indicate stones, masses, or vascular diseases.
- U/S of kidneys: used to evaluate for kidney size (useful to distinguish acute from chronic renal failure), to evaluate for the presence of obstruction, and to evaluate renal vascular status (w/Doppler evaluation).
- Renal CT: offers optimal imaging of the kidneys and bladder (trauma, nephrolithiasis, masses, infection, abscesses, hematuria).
- MRI: in subjects w/iodine allergy and renal failure, images the kidney and related structures. Cannot be used if pacemakers or metal clips are present.
- Renal bx: helpful as a dx tool for GN, SLE, nephrotic syndrome, RPGN, and AIN.

**Diagnostic Approach**
- A careful hx to demonstrate signs and sx of ARF: fatigue, nausea, SOB, vomiting, anorexia, weakness, change in diurnal sleep patterns, pruritus, muscle weakness, encephalopathy
- Focus hx on causes of prerenal azotemia (hypotension, bleeding, sepsis, CHF, diuretics and other causes of ↓ effective circulating volume); obstruction or intrinsic renal diseases (diabetes, contrast material, drugs, muscle trauma, vasculitis, GN).
- PE should assess volume status, arthritis, rashes (vasculitis, purpura), dyspnea, heart murmur, muscle injury, edema, fatigue, palpable bladder, uremic encephalopathy.

**Etiology**
- Prerenal: inadequate perfusion caused by hypovolemia, CHF, cirrhosis, sepsis. 60% of community-acquired cases of ARF are due to prerenal conditions.
- Postrenal: outlet obstruction from prostatic enlargement, ureteral obstruction (stones), tumors or neurogenic drugs. Postrenal causes account for 5%-15% of community-acquired ARF.
- Intrinsic renal: GN, ATN, drug toxicity (abx, nonsteroidal anti-inflammatory agent; hemodynamically active drugs such as ACEIs, ARBs, NSAIDs), contrast nephropathy, endogenous toxins (myoglobin, Hgb, uric acid), malignant HTN

**Treatment**
- Stop all nephrotoxic meds.
- Dietary modification to supply adequate calories while minimizing accumulation of toxins; appropriate control of fluid balance. Physicians should recommend a nutrition program w/an energy prescription of 120-150 kJ/kg/day and restriction of potassium (60 mEq/day), sodium
(90 mEq/day), and phosphorus (800 mg/day). Ideal protein supplementation ranges from 0.6-1.4 g/kg, depending on whether dialysis is required. In catabolic pts, dietary protein intake may be up to 200 g/day.

- Daily weight
- Modifications of dosage of renally excreted drugs
- Correct sx (N/V, fatigue) and lab abnormalities.
- Treat anemia w/erythropoiesis-stimulating agents, epoetin alfa, and darbepoetin alfa.
- Correct intravascular volume, fluid and electrolytes, BP.
- Prerenal: IV volume expansion in hypovolemic pts.
  - Closely restrict potassium, sodium, water intake, and acid-base parameters.
  - Restrict Mg intake to prevent toxicity and paralysis.
  - To prevent metastatic calcifications, treat hyperphosphatemia and hypocalcemia w/phosphate binders, vitamin D, oral Ca supplements when indicated, and dietary restriction of phosphorus.
- Intrinsic renal: discontinuation of any potential toxins and treatment of condition causing the renal failure.
  - Low-dose dopamine is at times used to influence renal dysfunction and may offer transient improvement in renal physiology; however, there is lack of evidence that it offers significant clinical benefits to pts w/or at risk for ARF.
  - Fenoldopam, a dopamine α1-receptor agonist currently approved for inpatient management of hypoperfusion states to ↑ renal blood flow
  - Although furosemide is used frequently to convert oliguric to nonoliguric renal failure in pts w/early ARF, it has no effect on mortality, dialysis requirement, and proportion of pts w/persistent oliguria. Its use in high dose is also associated w/↑ risk of tinnitus and temporary deafness.
- Postrenal: removal of obstruction

**Chronic Rx**

- Monitor renal function and electrolytes.
- Prevent further insults to the kidneys w/proper hydration, especially before contrast studies, and avoidance of nephrotoxic agents. Hydration w/sodium bicarbonate (addition of 154 mL of 1000 mEq/L sodium bicarbonate to 846 mL of D3W) before exposure to contrast material is more effective than hydration w/sodium chloride for prophylaxis of contrast–induced renal failure. After appropriate clinical evaluation and measurement of BP, pts should receive an initial IV bolus of 3 mL/kg/hr for 1 hr immediately before radiopaque injection and the same fluid at a rate of 1 mL/kg/hr during exposure to the contrast material and for 6 hr after the procedure.
- Treat w/dietary restriction and phosphate binders to normalize serum Ca and phosphorus.
- Administer erythropoiesis-stimulating agents, epoetin alfa and darbepoetin alfa, for target Hgb 11-12 g%.
- Daily hemodialysis is superior to every-other-day hemodialysis in pts w/ATN and ARF.

**Indications for Dialysis**

- Florid sx of uremia (encephalopathy, pericarditis)
- Significant derangement in electrolyte concentrations (e.g., hyperkalemia, hyponatremia)
- Severe volume overload
- Severe acid-base imbalance
- Should begin renal replacement Rx (hemodialysis, peritoneal dialysis, hemofiltration, CVVHD) before the severe adverse metabolic consequences of uremia occur
- Renal function recovery (ability to discontinue dialysis) varies from 50%-75% in survivors of ARF.
- Overall mortality rate in ARF is nearly 50%, varying from 60% in pts w/ATN to 35% in pts w/prerenal or postrenal ARF.
- The combination of ARF and sepsis is associated w/70% mortality rate.
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330  RENAL FAILURE, CHRONIC
Marc S. Weinberg

Definition
Chronic renal failure is a progressive ↓ in renal function (GFR <60 mL/min for >3 mo) w/subsequent accumulation of waste products in the blood, electrolyte abnormalities, and anemia.

Diagnosis

Clinical Presentation and Therapeutic Considerations
- The clinical presentation varies w/the degree of renal failure and its underlying cause. Common sx are generalized fatigue, nausea, anorexia, pruritus, insomnia, taste disturbances.
- Treatment of comorbidities may prolong the time necessary to initiate renal replacement Rx.
- Subjects w/chronic kidney disease, before stage IV (ESRD), require aggressive management to delay the progression by the following Rx: BP reduction w/use of ARBs or ACEIs; dietary management to control protein intake, serum glucose, Ca, potassium, and phosphorus.
- Erythropoiesis-stimulating agents should be started to ↓ sx and adverse outcomes of anemia.
- Indications for beginning hemodialysis
  - Salt and water overload, CHF, and pulmonary edema
  - Electrolyte abnormalities including hyperkalemia
  - Uncontrolled HTN
  - Signs and sx of uremia (ΔMS, encephalopathy, pericarditis)
  - Severe acid-base abnormalities, such as acidosis
  - Skin pallor, ecchymoses

Labs
- BUN, Cr, CrCl
- U/A: may reveal proteinuria, renal tubular cells, or cellular casts such as WBC or RBC casts
- Serum chemistry: ↑ BUN and Cr, hyperkalemia, hyperuricemia, hypocalcemia, hyperphosphatemia, hyperglycemia, ↓ bicarbonate
- Measure urinary protein excretion. The finding of a ratio of protein to Cr of >1000 mg/g suggests the presence of glomerular disease.
- Special studies: serum and urine IEP (in suspected MM, light chain, Bence Jones, and monoclonal gammopathy-related diseases), ANA (in suspected SLE), HIV (AIDS nephropathy), complement and blood cultures in subacute bacterial endocarditis–induced proliferative GN and eosinophilia or eosinophiluria associated w/AIN.
- Cystatin C is a cysteine proteinase inhibitor produced by all nucleated cells, freely filtered at the glomerulus but not secreted by tubular cells. Given these characteristics, it may be superior to Cr concentration both in kidney disease and as a marker of acute kidney injury. It is a better index of kidney function in elderly pts and a better predictor of outcomes than Cr is. The association of cystatin C is stronger than the association of measured GFR w/all-cause and CVD mortality in pts w/advanced chronic kidney disease.

Imaging
- U/S of kidneys to measure kidney size and r/o obstruction

Diagnostic Approach
- Lab eval and imaging studies should be aimed at identifying reversible causes of acute decrements in GFR (e.g., volume depletion, urinary tract obstruction, CHF) superimposed on chronic renal disease.
- Kidney bx: generally not performed in pts w/small kidneys or w/advanced disease
- GFR: best overall indicator of kidney function. It can be estimated by prediction equations that take into account the serum Cr level and some or all of specific variables (body size, age, sex, race). GFR calculators are available on the National Kidney Foundation website [http://www.kidney.org/kfs/professionals/gfr_calculator.cfm].
- Cockcroft-Gault formula is most common and uses age, weight, plasma Cr, and gender.
Etiology
- Diabetes (>40%), HTN (30%), chronic GN (>12%), adult polycystic kidney disease, HIV nephropathy
- Tubular interstitial nephritis (e.g., drug hypersensitivity, analgesic nephropathy), obstructive nephropathies (e.g., nephrolithiasis, prostatic disease)
- Vascular diseases (RAS, hypertensive nephrosclerosis)

Treatment
- Provide adequate nutrition and calories (147-168 kJ/kg/day in energy intake, chiefly from carbohydrate and polyunsaturated fats). Referral to a dietitian for nutritional Rx for pts w/GFR <50 mL/1.73 m² is recommended.
- Restrict sodium (approximately 100 mmol/day), potassium (<60 mmol/day), and phosphate (<800 mg/day).
- Adjust drug doses to correct for prolonged half-lives.
- Restrict fluid if significant edema or hyponatremia is present.
- Protein restriction (<8 g/kg/day) may slow deterioration of renal function; however, studies have not confirmed this benefit. There is insufficient evidence to recommend or to advise against routine restriction of protein intake. Protein restriction may impair the benefits of good nutrition and nl plasma renal alb levels and also be of very minor importance in subjects treated with renin-angiotensin system blockers (ARBs, ACEIs, and renin inhibitors).
- Resistance exercise training can preserve lean body mass, nutritional status, and muscle function in pts w/moderate chronic kidney disease.
- Avoid radiocontrast agents. Hydration w/sodium bicarbonate before exposure to contrast material is more effective than hydration w/sodium chloride for prophylaxis of contrast-induced renal failure. Mucomyst and CCBs have been used to prevent radiocontrast-induced ARF, but beneficial studies are not definitive.
- Smoking cessation
- Initiate hemodialysis or peritoneal dialysis before sx of uremia occur (for diabetic subjects, CrCl of 15 mL/min; nondiabetics start at 10 mL/min).
- Pts w/signs or sx of uremia or other indications need to have renal replacement Rx initiated earlier (CHF, asterixis, encephalopathy, hyperkalemia, nausea, pruritus).
- Prompt referral to a nephrologist is essential. Late evaluation of pts w/chronic renal disease is associated w/greater burden and severity of comorbid disease and shorter survival.
- Kidney transplantation in selected pts
- ACEIs: useful in reducing proteinuria and slowing the progression of chronic renal disease, especially in HTN diabetic pts. A systolic BP between 110-129 mm Hg may be beneficial in pts w/urine protein excretion >1.0 g/day. Systolic BP <110 mm Hg may be associated w/a higher risk for kidney disease progression.
- Urgent indications for the initiation of dialysis: uremic pericarditis, neuropathy, seizures, encephalopathy, neuromuscular abnormalities, CHF, hyperkalemia, severe acidosis, refractory nausea, itching, or fatigue
- Judgmental indications: CrCl 10-15 mL/min; progressive anorexia, weight loss or loss of appetite, reversal of nl diurnal sleep patterns, pruritus, uncontrolled fluid gain w/HTN and signs of CHF
- Erythropoiesis-stimulating agents, epoetin alfa and darbepoetin alfa, can be used to ↓ the need for transfusions in pts w/anemia. Anemia should not be fully corrected in pts w/chronic kidney disease. Maintenance of a target Hgb of 11-12 g/dL or Hct 30%-33% is satisfactory because studies suggest ↑ CV mortality in subjects w/Hgb >13.5%.
- Loop diuretics for significant fluid overload (thiazides will not work for GFR <25 mL/min)
- Correction of HTN to at least 130/85 mm Hg w/ACEIs (avoid in pts w/significant hyperkalemia, pregnancy, or angioedematous edema), ARBs (not in pregnancy), or nondihydropyridine CCBs (verapamil, diltiazem) in pts intolerant of ACEIs or when other agents are needed to control BP
- Correction of electrolyte abnormalities (e.g., Ca chloride, glucose, sodium polystyrene sulfonate for hyperkalemia), sodium bicarbonate in pts w/severe metabolic acidosis
Lipid-lowering agents in pts w/dyslipidemia; target LDL cholesterol is <100 mg/dL (in cardiac disease, LDL <70 mg/dL). Because the primary mortality is CV in subjects w/ESRD, all CV risk factors should be aggressively treated.

Control of renal osteodystrophy w/Ca supplementation and vitamin D. Starting dose of Ca carbonate is 0.5 g w/each meal, ↑ until the serum phosphorus concentration is normalized (most pts require 5-10 g/day). Calcitriol 0.125-0.25 μg/day PO is effective in ↑ serum Ca concentration. Paricalcitol and cinacalcet HCl, new vitamin D analogues, have been reported as more effective than calcitriol in preventing side effects of hypercalcemia.

Sevelamer and lanthanum are useful phosphate binders to ↓ serum phosphate levels w/o the severe metastatic calcifications associated w/the administration of Ca phosphate binders.

**Prognosis**

- Prognosis is influenced by comorbidity of multisystem diseases. Late referral of pts to a nephrologist is associated w/↑ mortality, morbidity, and costs. Despite recommendations for early referral, up to 64% of pts w/chronic renal failure are still referred late.
- Aggressive management of CVD risk factors may lessen the ↑ mortality and morbidity observed in subjects w/ESRD.
- Kidney transplantation in selected pts. The 2-yr kidney graft survival rate for living related donor transplantations is >80%, whereas the 2-yr graft survival rate for cadaveric donor transplantation is approximately 70%.

### 331 RENAL TUBULAR ACIDOSIS (RTA)

**Definition**

Disorder characterized by inability to excrete H+ or inadequate generation of new HCO3-. There are 4 types of renal tubular acidosis:

- Type 1 (classic, distal RTA): abnormality in distal hydrogen secretion resulting in hypokalemic hyperchloremic metabolic acidosis.
- Type 2 (proximal RTA): ↓ proximal bicarbonate reabsorption resulting in hypokalemic hyperchloremic metabolic acidosis.
- Type 3 (RTA of glomerular insufficiency): normokalemic hyperchloremic metabolic acidosis as a result of impaired ability to generate sufficient NH3 in the setting of ↓ GFR (<30 mL/min). This type of RTA is described in older textbooks and is considered by many not to be a distinct entity.
- Type 4 (hyporeninemic hypoaldosteronemic RTA): aldosterone deficiency or antagonism resulting in ↓ distal acidification and ↓ distal sodium reabsorption w/subsequent hyperkalemic hyperchloremic acidosis.

**Diagnosis**

**Labs**

- ABGs: metabolic acidosis
- Serum potassium is low in RTA types 1 and 2, nl in type 3, and high in type 4.
- Min. urine pH is >5.5 in RTA type 1, <5.5 in types 2, 3, and 4.
- Urinary AG is 0 or + in all types of RTA.
- Additional useful studies include serum Ca level and urine Ca.
- AG is nl.
- PTH measurement: useful in pts suspected of primary hyperparathyroidism (may be associated w/type 2 RTA)

**Imaging**

- Renal U/S or non-contrast-enhanced helical CT of abd can be used to evaluate renal size or presence of stones.

**Etiology**

- Type 1 RTA: autoimmune disorders, PBC and other liver diseases, meds (amphotericin, NSAIDs), SLE, SS, genetic disorders (Ehlers-Danlos syndrome, Marfan syndrome, hereditary elliptocytosis), toxins (toluene), disorders w/neophocalcinosis (hyperparathyroidism, vitamin D intoxication, idiopathic hypercalciuria), tubulointerstitial disease (obstructive uropathy, renal transplantation)
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- Type 2 RTA: Fanconi’s syndrome, primary hyperparathyroidism, MM, medications (acetazolamide)
- Type 4 RTA: DM, sickle cell disease, Addison’s disease, urinary obstruction

Treatment
- Type 1 and type 2: oral sodium bicarbonate (1-2 mEq/kg/day in type 1 RTA, 2-4 mEq/kg/day in type 2 RTA) titrated to correct acidosis
- Potassium supplementation in hypokalemic pts
- Type 4 RTA: furosemide to lower elevated potassium levels and sodium bicarbonate to correct significant acidosis. Fludrocortisone 100-300 µg/day can be used to correct mineralocorticoid deficiency.

Clinical Pearl
- Untreated distal RTA may result in hypercalcemia, hyperphosphaturia, nephrolithiasis, and nephrocalcinosis.

332 RENAL VEIN THROMBOSIS

Definition
Thrombotic occlusion of one or both renal veins.

Diagnosis
H&P
- Clinical presentation: flank pain, renal failure, hematuria, edema, DVT of LEs, dilated abd pains, back pain

Imaging
- Abd U/S
- Abd MRI
- Renal arteriography (delayed films during venous phase)
- Selective renal vein venography (inferior venacavogram images should be obtained before the catheter is advanced in the vena cava because clots, if present, could be dislodged)

Etiology
- Extrinsic compression by a tumor or retroperitoneal mass
- Invasion of the renal vein or IVC by tumor (almost always renal cell cancer)
- Trauma
- Hypercoagulable states
- Dehydration
- Glomerulopathies (membranous GN, crescentic GN, SLE, amyloidosis), especially in the presence of nephrotic syndrome when the serum alb is <2 g/dL

Treatment
- Anticoagulation in acute thrombosis
- Thrombolytic Rx or surgical thrombectomy also effective
- The value of anticoagulation in chronic renal vein thrombosis is dubious except in nephrotic pts w/membranous GN w/profound hypoalbuminemia.

333 RHABDOMYOLYSIS

Definition
Acute or subacute event resulting in damage or necrosis of striated muscle.

Diagnosis
H&P
- Variable muscle tenderness. Rhabdo apart from statin use is manifested w/muscle sx only 50% of the time.
- Weakness
- Muscle rigidity
- Fever
- Altered consciousness
- Muscle swelling
- Malaise, fatigue. In statin-induced rhabdo, fatigue (74%) is nearly as common as muscle pain (88%).
- Dark urine
Labs

- **↑↑ CK**: elevations may exceed 100,000 U/L in fulminant rhabdo; the development of renal failure is not directly related to the threshold level of CK; isoenzyme fractionation is useful: if CK-MB exceeds 5% of the total CK, involvement of the myocardium is likely.

- **↑ Serum Cr**: etiology of the renal failure is uncertain and probably multifactorial (renal tubular obstruction by precipitated myoglobin, direct myoglobin toxicity, hypotension, dehydration, ↓ GFR, intravascular coagulation).

- Serum potassium: preexisting hypokalemia is a contributing factor to rhabdo; fulminant rhabdo can result in life-threatening hyperkalemia secondary to ↑ K+ release from damaged muscle and impaired renal excretion.

- Ca and phosphate: initially there is hyperphosphatemia from muscle necrosis, secondary hypocalcemia from Ca2+ deposition in the injured muscle, and ↓ 1,25-dihydroxycholecalciferol; later (in the diuretic phase of renal failure), hypercalcemia is present as a result of remobilization of the deposited Ca2+ and secondary hyperparathyroidism.

- Myoglobin: present in the serum and urine; the urine is brownish, has granular casts, and is o-toluidine positive; a quick visual method to separate myoglobinuria from hemoglobinuria is to examine the urine and serum simultaneously: reddish brown urine and pink serum indicate hemoglobinuria, whereas brown urine and clear serum suggest myoglobinuria; a rise in serum myoglobin precedes the rise in CK level and is useful to estimate the risk of renal failure (serum myoglobin levels >2000 μg/L may be associated w/renal insufficiency).

Etiology

- **Trauma** (e.g., crush syndrome, burns, electrical shock)

- **Muscle ischemia** (e.g., thrombosis, embolism, vasculitis, sickle cell disease, pressure necrosis, tourniquet shock)

- **Drugs**: drug-induced rhabdo can occur through several mechanisms.
  - Primary, toxin induced (e.g., ethanol, methadone, ethylene glycol, isopropyl alcohol, CO poisoning)
  - Caused by chronic intake of drugs associated w/hypokalemia (e.g., thiazides)
  - Caused by OD of certain drugs (e.g., barbiturates, heroin, cocaine)
  - Malignant hyperthermia (usually seen in genetically predisposed individuals, after exposure to halothane, succinylcholine, or pancuronium)
  - NMS (associated w/use of phenothiazines, butyrophenones, antipsychotics, cocaine, or diphenhydramine, usually in pts w/dehydration and electrolyte imbalance)
  - Use of certain lipid-lowering agents (e.g., combination of statins and gemfibrozil, fenofibrate, or erythromycin; simvastatin and amiodarone; amphetamines, haloperidol)
  - Direct myotoxicity (e.g., colchicine, zidovudine, cyclosporine,itraconazole)

- **Infections**.
  - Bacterial (e.g., *Streptococcus*, *Salmonella*, *Clostridium*, *Legionella*, *Leptospora*, *Shigella*)
  - Viral (e.g., echo, coxsackie, influenza, CMV, herpes, EBV, hepatitis)
  - Parasites (trichinosis)

- Excessive muscle stress (e.g., marathon runners, status epilepticus, delirium tremens)

- Genetic defects (carnitine deficiency, phosphorylase deficiency, glucosidase deficiency, cytochrome disturbances)

- Miscellaneous: brown recluse spider bite, snake bite, hornet sting, polymyositis, dermatomyositis, heat stroke, DKA, hyponatremia, hypophosphatemia, myxedema, thyroid storm, RMSF, hypothermia, CO, cyclic antidepressants, phenylpropanolamine, codeine, phencyclidine (PCP), amphetamines, LSD, Reye’s syndrome
Treatment
- Vigorous fluid replacement to maintain a good urinary output, at least until myoglobin disappears from the urine. Initially NS should be given at a rate of 1.5 L/hr w/close monitoring of cardiac, pulmonary, and electrolyte status. Maintain ↑ rate of IV fluids at least until CPK <1000 U/L. Pts may require >15 L of fluid in the initial 24 hr to achieve urine flow rates of 200-300 mL/hr.
- Administration of a single dose of mannitol (100 mL of a 25% solution IV during 15 min) remains controversial. Mannitol acts as an osmotic diuretic, renal vasodilator, and intravascular volume expander and may convert oliguric renal failure to nonoliguric.
- Alkalization of the urine w/addition of 44 mEq/L of sodium HCO₃ is advocated by some experts. The goal is to maintain urine pH >6.5. Sodium bicarbonate may ↑ solubility of uric acid and myoglobin; however, it may promote Ca deposition.
- Hyperkalemia caused by rhabdo is most severe 10-40 hr after injury; initial treatment w/sodium polystyrene sulfonate may be indicated; hyperkalemia caused by rhabdo responds poorly to treatment w/glucose and insulin; attempts to correct hyperkalemia and initial hypocalcemia w/Ca infusion may result in metastatic calcifications and severe hypercalcemia in the recovery period; hemodialysis may be necessary in pts w/severe hyperkalemia, volume overload, uremic pericarditis, or uremic encephalopathy.

Clinical Pearls
- The average length of time on statin Rx before rhabdo is 1 yr. Average time to onset of rhabdo after addition of fibrate to statin Rx is 32 days.
- Statin-induced rhabdo is 12× more frequent when statins are combined w/fibrates compared w/statin monotherapy.

334 RHEUMATOID ARTHRITIS (RA)
Definition
Inflammatory disease that affects primarily synovium-lined joints but also can affect the cardiac, nervous, pulmonary, reticuloendothelial, and integumentary systems. RA is a clinical dx. The 7 criteria of the American College of Rheumatology are
- Morning stiffness in or around joints lasting at least 1 hr before improvement
- Arthritis of 3 or more joint areas
- Arthritis of hand joints w/at least one swollen area in a wrist, MCP, or PIP joint
- Symmetric arthritis
- Presence of rheumatoid nodules (SC nodules over bone prominences or extensor surfaces or juxta-articular regions)
- Positive serum RF
- Typical radiographic changes (erosions or bone calcifications localized in or most marked adjacent to involved joints)
Existence of ≥4 of these criteria denotes RA.

Diagnosis
H&P
The initial manifestations of RA are highly variable. In the majority of pts, the onset is insidious, taking months or years to become clinically evident as a diagnosable entity. In other pts, the onset is dramatic w/rapid development of severe manifestations (see following). RA can present w/any of the following articular and extra-articular manifestations:
- Articular and periarticular manifestations
  - Morning stiffness is often the initial complaint, usually lasting longer than in osteoarthritis.
  - Symmetric polyarthritis
  - Joint swelling and tenderness to palpation, w/significant limitation of motion of involved joints
- Commonly involved joints in pts w/RA are metacarpophalangeal, metatarsophalangeal, proximal interphalangeal (PIP), wrist, knee, ankle, shoulder, and hip; however, any joint in the body can be affected.
- Joint deformities generally result from hyperextension or flexion of the joints.
  - Hyperextension of PIP joints and flexion of distal interphalangeal (DIP) joints (swan-neck deformity)
  - Flexion of PIP joints and extension of DIP joints (boutonnière deformity)
- Others: knee and ankle effusions, hoarseness secondary to cricoarytenoid arthritis, myelopathy secondary to nerve compression
- Atlantoaxial subluxation can occur in up to 30% of pts and can lead to spinal cord compression if it is not promptly dx and treated. The dx is especially important in pts undergoing surgery because of the danger of neck extension during anesthesia causing spinal cord damage.

**Extra-articular manifestations**
- Pulmonary involvement consists of one or more of the following:
  - Pulmonary nodules; association of rheumatoid pulmonary nodules and interstitial pneumoconiosis is known as *Caplan’s syndrome*; pulmonary nodules are usually multiple, as opposed to the single nodules seen w/lung carcinoma.
  - Pleural effusions (exudative w/low glucose concentration)
  - Pulmonary vasculitis
  - Pleuritis
- Ocular involvement: scleritis, episcleritis; RA is often associated w/SS.
- Vasculitis is generally seen in pts w/↑↑ titers of RF; it can involve any organ, and frequent manifestations are mononeuritis multiplex (e.g., footdrop or wristdrop) and digital arteritis.
- Hematologic abnormalities
  - Normochromic normocytic or microcytic anemia (multifactorial: chronic disease, blood loss resulting from use of salicylates and NSAIDs)
  - Granulocytopenia: the presence of granulocytopenia and splenomegaly in RA is known as *Felty’s syndrome*; it affects 1% of pts w/RA and is associated w/an ↑ risk of infection and NHL.
  - Hyperviscosity, cryoglobulinemia
- Cardiac involvement: pericarditis, conduction defects, myocarditis, arteritis
- Skin: SC nodules (caused by granulomatous inflammation of surrounding arteries) may be found over the olecranon process and any bone prominences.
- Constitutional sx: fever, weight loss, anorexia, malaise
- Others: osteoporosis, myositis, compressive neuropathies, amyloidosis, mesangial glomerulonephrosis

**Labs**
There is no isolated lab test that can exclude or prove the dx of RA. Any of the following laboratory abnormalities may be present:
- RF: latex positivity may be initially absent (− in 30% of pts early in illness), but during the course of the disease, approximately 85% of pts become latex +; RF is not specific for RA and can be found in other conditions (e.g., osteomyelitis, infective endocarditis, liver disease, and nonspecific elevation in the elderly).
- ESR, CRP: generally ↑ during exacerbations and can be used to monitor disease course
- ANA: detected in 15% of pts, has limited value as a screening test
- ↓ Hgb/Hct (normocytic or microcytic anemia), granulocytopenia or ↑ WBC, ↑ platelets
- NI or ↑ alk phos
- Anti–cyclic citrullinated peptide Ab: it is less sensitive but more specific than RF and correlates well w/disease progression.

**Imaging**
Initially, soft tissue swelling may be the only manifestation. As the disease progresses, there is periarticular osteopenia, cortical thinning, and marginal
erosion. Subluxation and joint space diminution are late findings. Wrist and ankle films are useful as baselines for comparison w/future studies.

**Treatment**

- There are two major categories of drugs:
  - Rapid acting: NSAIDs and systemic corticosteroids
  - DMARDs should be considered for all pts w/RA. Early initiation of DMARDs is recommended.
- Most clinicians begin Rx w/DMARD (hydroxychloroquine or sulfasalazine for mild forms of RA, or MTX in more severe disease) in addition to an NSAID or a corticosteroid. Combination DMARD Rx (e.g., MTX and leflunomide) can also be used in cases of moderate to severe disease. Etanercept, infliximab, adalimumab, and abatacept are effective newer agents.

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**335 SALICYLATE POISONING**

**Diagnosis**

*H&P*

- N/V, tinnitus, seizures, hyperventilation, hemorrhage
- Polyuria may be followed by oliguria

*Labs*

- Most common manifestation is combined metabolic acidosis and respiratory alkalosis, although either one can occur.
- AG acidosis may develop.
- Hypokalemia may develop.

**Treatment**

- Removal of salicylates by alkaline diuresis
- IV bolus NaHCO₃, 2 mEq/kg IV push, then start maintenance infusion (152 mEq NaHCO₃ in 1 L D₂W at 250 mL/hr)
- Administration of activated charcoal (1 g/kg; max: up to 50 g PO) in water or sorbitol by NG tube
- Gastric lavage, osmotic diuresis, and dialysis in cases of severe intoxication (serum salicylate level >70 mg/dL)

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**336 SARCOIDOSIS**

**Definition**

Chronic systemic granulomatous disease of unknown cause, characterized histologically by the presence of nonspecific, noncaseating granulomas.

**Diagnosis**

*H&P*

Clinical manifestations often vary w/stage of the disease and degree of organ involvement; pts may be asymptomatic, but CXR may demonstrate findings consistent w/sarcoidosis (see Imaging). Nearly 50% of pts w/sarcoidosis are dx by incidental findings on CXR. Frequent manifestations:

- Pulmonary manifestations: dry, nonproductive cough; dyspnea; chest discomfort
- Constitutional sx: fatigue, weight loss, anorexia, malaise
- Visual disturbances: blurred vision, ocular discomfort, conjunctivitis, iritis, uveitis (65% of pts)
- Dermatologic manifestations: erythema nodosum (10% of pts), macules, papules, SC nodules, hyperpigmentation, lupus pernio (indurated violaceous lesions on the nose, lips, ears, cheeks that can erode into underlying cartilage and bone)
- Myocardial disturbances (5% of pts): arrhythmias, cardiomyopathy
- Splenomegaly, hepatomegaly
- Rheumatologic manifestations: arthralgias have been reported in up to 40% of pts
- Neurologic and other manifestations: cranial nerve palsies, diabetes insipidus, meningeal involvement, parotid enlargement, hypothalamic and pituitary lesions, peripheral adenopathy

*Labs*

- Hypergammaglobulinemia, anemia, leukopenia
- LFT abnormalities
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- Hypercalcemia (11% of pts), hypercalciuria (40% of pts): due to ↑ GI absorption, abnl vitamin D metabolism, and ↑ calcitriol production by sarcoid granuloma
- ↑ ACE in 60% of pts; nonspecific and generally not useful as a dx tool and in following the course of the disease

**Imaging**
- CXR and chest CT
  - Adenopathy of the hilar and paratracheal nodes
  - Parenchymal changes may also be present, depending on the stage of the disease: stage 0, nl x-ray; stage I, bilateral hilar adenopathy; stage II, stage I plus pulmonary infiltrate; stage III, pulmonary infiltrate w/o adenopathy; stage IV, advanced fibrosis w/evidence of honeycombing, hilar retraction, bullae, cysts, and emphysema
- PFTs (spirometry and diffusing capacity of the lung for CO): may be nl or may reveal a restrictive pattern or obstructive pattern
- $^{18}$FDG-PET: useful in identifying sites for dx bx in pts w/o apparent lung involvement
- $^{18}$FDG-PET and MRI w/gadolinium: useful in pts w/suspected cardiac and neurologic involvement
- Gallium Ga 67 scan: older testing modality. It will localize in areas of granulomatous infiltrates; the “panda” sign (localization in the lacrimal and salivary glands, giving a “panda” appearance to the face) is suggestive of sarcoidosis.

**Treatment**
- Many pts will not require any treatment.
- Corticosteroids should be considered in pts w/severe sx (e.g., dyspnea; chest pain; hypercalcemia; ocular, CNS, or cardiac involvement; and progressive pulmonary disease).
- MTX 7.5-15 mg once/wk: in pts w/progressive disease refractory to corticosteroids
- Hydroxychloroquine: effective for chronic disfiguring skin lesions, hypercalcemia, and neurologic involvement
- NSAIDs: useful for musculoskeletal sx and erythema nodosum
- Consider liver and lung transplantation in pts unresponsive to conventional treatment.

**Clinical Pearls**
- The majority of pts w/sarcoidosis have spontaneous remission within 2 yr and do not require treatment. Their course can be followed by periodic clinical evaluation, CXR, and PFTs.
- 25%-33% of pts have unrelelenting disease, leading to clinically significant organ impairment. Adverse prognostic factors are age at onset >40 yr, cardiac involvement, neurosarcoidosis, progressive pulmonary fibrosis, chronic hypercalcemia, chronic uveitis, involvement of nasal mucosa, nephrocalcinosis, and presence of cystic bone lesions and lupus pernio.

### 337 SCABIES

**Definition**
Contagious disease caused by the mite *Sarcoptes scabiei*.

**Diagnosis**
- Dx is made on the clinical presentation and on the demonstration of mites, eggs, or mite feces.
- Primary lesions are caused when the female mite burrows within the stratum corneum, laying eggs within the track she leaves behind; burrows (linear or serpiginous tracks) end w/a minute papule or vesicle.
- Primary lesions are most commonly found in the web spaces of the hands, wrists, buttocks, scrotum, penis, breasts, axillae, and knees.
- Secondary lesions result from scratching or infection.
- Intense pruritus, especially nocturnal, is common 1-4 wk after the primary infestation; it is due to an acquired sensitivity to the mite or fecal pellets.
- Exam of the skin may reveal burrows, tiny vesicles, excoriations, inflammatory papules.
Microscopic demonstration of the organism, feces, or eggs: a drop of mineral oil may be placed over the suspected lesion before removal; the scrapings are transferred directly to a glass slide; a drop of potassium hydroxide is added, and a cover slip is applied.

**Treatment**
- Permethrin 5% cream is effective w/usually one treatment; it should be massaged into the skin from head to soles of feet; remove 8-14 hr later by washing. If living mites are present after 14 days, treat again.
- A single dose (150-200 µg/kg in 6-mg tablets) of ivermectin, an anthelmintic agent, is also effective for the treatment of scabies.
- Pruritus generally abates 24-48 hr after treatment, but it can last up to 2 wk; oral antihistamines are effective in ↓ post scabietic pruritus.
- Topical corticosteroid creams may hasten the resolution of secondary eczematous dermatitis.
- If the pt is a resident of an extended care facility, it is important to educate the pts, staff, family, and frequent visitors about scabies and the need to have full cooperation in treatment. Scabicide should be applied to all pts, staff, and frequent visitors, whether symptomatic or not; symptomatic family members of staff and visitors should also receive treatment.

**Clinical Pearls**
- Scabies is generally acquired by sleeping w/or in the bedding of infested individuals.
- Widespread and crusted lesions (*Norwegian or crusted scabies*) may be seen in elderly and immunocompromised pts.

### SCLERODERMA (SYSTEMIC SCLEROSIS)

**Definition**
Connective tissue disorder characterized by thickening and fibrosis of the skin and variably severe involvement of diverse internal organs.

**Diagnosis**

**H&P**
- **Skin:**
  - Begins on hands, then face; skin is shiny, taut, sometimes red w/loss of creases and hair
  - Later skin tightening may limit movement.
  - Pigmentary changes occur.
  - Skin atrophy occurs in late stages.
- **Musculoskeletal:**
  - Symmetric inflammatory arthritis
  - Myopathy
- **GI:**
  - Esophageal dysmotility w/heartburn, dysphagia, odynophagia
  - Delayed gastric emptying
  - Small bowel dysmotility w/abd cramps and diarrhea
  - Colon dysmotility w/constipation
- **Pulmonary:**
  - Pulmonary fibrosis w/sx of dyspnea and nonproductive cough and fine inspiratory crackles on exam
  - Pulmonary HTN
- **Cardiac involvement:** myocardial fibrosis leading to CHF
- **Renal:**
  - Malignant HTN
  - Rapidly progressive renal failure
- **Other:**
  - Hypothyroidism
  - Erectile dysfunction
  - SS
  - Entrapment neuropathies
  - CREST syndrome: calcinosis, Raynaud’s syndrome, esophageal dysmotility, sclerodactyly, telangiectasias (in CREST, scleroderma is limited to distal extremities)
### Seizure Disorder, Absence

#### Definition
Absence seizures are a type of generalized nonconvulsive seizure characterized by episodes of loss of awareness (typically ≤10 sec) associated with a 3-Hz generalized spike and slow-wave EEG pattern, followed by abrupt return to full consciousness.

#### Diagnosis

**H&P**
- Findings are nl between seizures in children with typical absence epilepsy.
- During seizure, pt typically appears awake but abruptly ceases ongoing activity and does not respond to or recall stimuli.
- More prolonged episodes may be associated with automatisms and therefore be mistaken for complex partial seizures.
- Tonic-clonic seizures can occur in approximately 40% of pts.
**EEG**
- Most powerful tool for identification of this seizure type. Hyperventilation for 3-5 min provokes characteristic EEG finding.

**Etiology**
- Idiopathic w/ a presumed genetic cause
- Absence seizures can also be seen w/ some types of generalized epilepsy syndromes, such as juvenile absence epilepsy and juvenile myoclonic epilepsy.

**Treatment**
- Drug of choice is ethosuximide or valproate.
- Ethosuximide does not suppress tonic-clonic seizures. Thus, valproate is the drug of choice for pts w/ coexisting absence and tonic-clonic seizures.
- Because most pts will have spontaneous resolution of their seizures, one can consider withdrawal of anticonvulsant Rx when the pt has been seizure free for at least 2 yrs and EEG is nl.

### SEIZURE DISORDER, PARTIAL

**Definition**
In partial seizures, the onset of abnl electrical activity originates in a focal region or lobe of the brain. Clinical manifestations may involve sensory, motor, autonomic, or psychic sx. Consciousness may be preserved (simple partial seizures) or impaired (complex partial seizures).

**Diagnosis**

**H&P**
- Clinical presentation is variable and depends on the site of origin of the abnl electrical d/cs.
- Sx of simple partial seizures can include focal motor or sensory sx; language disturbance; olfactory, visual, or auditory hallucinations; visceral sensations; and fear or panic.
- With complex partial seizures, there is a loss or reduction of awareness. This may be preceded by an aura (simple partial seizure). There may be associated automatisms or alterations in behavior.
- There may be a relatively quick “march” or progression of sx during seconds to minutes as the ictal focus spreads along the cortex.

**Imaging**
- EEG: most powerful tool for localization of the seizure focus
- MRI w/ contrast

**Etiology**
- Seizures are a sx of an underlying abnormality affecting the CNS, not a disease.
- Partial-onset seizures may be caused by underlying disorders including stroke, tumor, infection, trauma, vascular malformations, and genetic factors.

**Treatment**
- Individual seizures lasting <5 min require no acute pharmacologic intervention.
- Treatment is indicated if there is a significant risk of recurrence or the pt has experienced more than one unprovoked seizure.
- Phenytoin, carbamazepine, and valproate are traditional therapeutic agents but are limited by drug interactions and side effects.
- Newer agents such as lamotrigine, topiramate, oxcarbazepine, zonisamide, gabapentin, levetiracetam, and pregabalin have fewer drug interactions and are generally better tolerated, particularly in the elderly population.

### SEPSIS/SEPTIC SHOCK

**Definition**
- **Bacteremia:** presence of viable bacteria in the blood as evidenced by a positive blood culture; bacteremia can be one of the following:
  - Transient (e.g., dental extractions)
  - Continuous or sustained (e.g., bacterial endocarditis or abscess)
  - Intermittent (e.g., intermittent biliary tract obstruction)
**Chapter 3 Diseases and Disorders**

- **Septicemia**: bacteremia w/clinical manifestations (fever, chills)
- **Systemic inflammatory response syndrome**: systemic response manifested by two or more of the following:
  - Temperature >38°C (100.4°F) or <36°C (98.6°F)
  - RR ≥20 breaths/min or CO₂ <32 mm Hg
  - HR >90 bpm
  - WBC >12,000/µL or <4000/µL, or presence of >10% immature neutrophils (“bands”)
- **Septic shock**: life-threatening bacteremia manifested as hypotension despite adequate fluid resuscitation, and possibly oliguria, lactic acidosis, and acute ΔMS

**Diagnosis**

**H&P**

- **Early phase**
  - Hypotension
  - Hyperventilation (respiratory alkalosis)
  - Skin warm, dry
  - Subtle ΔMS
  - Fever (may not be present in elderly or chronically ill pts; some of these pts may actually manifest hypothermia)
  - Chills: generally occur 1 hr after the acute episode of bacteremia at a time when the host has cleared the bloodstream of bacteria; the highest yield for blood cultures is before the onset of chills.
  - Labs: minor ↑ or ↓ in WBC or neutrophil percentage, ↑ blood glucose levels
  - Hemodynamic monitoring: ↓ PCWP and SVR, ↑ CO

- **Late phase**
  - Significant hypotension
  - Skin cool and clammy
  - Oliguria
  - Metabolic acidosis (secondary to lactic acidosis), DIC, ↑ LFTs, renal failure, hypoglycemia
  - Hemodynamic monitoring: ↓ PCWP and CO, ↑ SVR

**Labs**

- CBC w/diff, blood and urine cultures, cultures of suspected foci

**Etiology**

- Gram-negative bacilli (*E. coli, Pseudomonas, Proteus, Klebsiella, Enterobacter, Serratia*, meningococcus)
- Gram-positive organisms (*S. aureus, pneumococci, streptococci*)
- Fungal infections

**Sites of Infection**

- GU tract (most common site of sepsis in the elderly)
- GI tract
- Respiratory tract
- Wounds, infected IV lines
- Meninges

**Predisposing Factors**

- Malnutrition
- Instrumentation or other invasive procedures
- Advanced age
- Immunosuppressive Rx
- Neoplastic diseases
- Chronic diseases such as DM or renal failure

**Treatment**

- IV empiric abx options for pts w/sepsis are described in Table 3-39.
- Treat hypotension w/NS infusion; aggressive volume resuscitation is one of the first critical steps. In pts w/hemodynamic monitoring, titrate fluid infusion volumes to obtain a PCWP of 15-18 mm Hg. If CVP from central lines is used, the goal is a CVP of 10-15.
- Colloid plus crystalloid solutions may occasionally be necessary in selected pts.
### TABLE 3-39  Empiric Antibiotic Options for Patients with Severe Sepsis or Septic Shock

<table>
<thead>
<tr>
<th>Suspected Source</th>
<th>Lung</th>
<th>Abdomen</th>
<th>Skin or Soft Tissue</th>
<th>Urinary Tract</th>
<th>Meninges</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major community-acquired pathogens</strong></td>
<td>Streptococcus pneumoniae</td>
<td>Haemophilus influenzae</td>
<td>Chlamydophila pneumoniae</td>
<td>Streptococcus pyogenes</td>
<td>E. coli</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli</td>
<td>Bacteroides fragilis</td>
<td></td>
<td>Staphylococcus aureus</td>
<td>Klebsiella species</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Polymicrobial</td>
<td>Enterobacter species</td>
</tr>
<tr>
<td><strong>Empiric antibiotic therapy</strong></td>
<td>Moxifloxacin or gatifloxacin or azithromycin plus either cefotaxime or ceftazidime</td>
<td>Imipenem-cilastatin or meropenem or piperacillin-tazobactam ± aminoglycoside</td>
<td>Vancomycin plus imipenem or meropenem or piperacillin-tazobactam</td>
<td>Ciprofloxacin or levofloxacin (if gram-positive cocci, use ampicillin plus gentamicin)</td>
<td>Vancomycin plus either ceftriaxone or cefepime</td>
</tr>
<tr>
<td><strong>Major commensal or nosocomial microorganisms</strong></td>
<td>Aerobic gram-negative bacilli</td>
<td>Aerobic gram-negative rods Anaerobes Candida species</td>
<td>Staphylococcus aureus (?MRSA)</td>
<td>Aerobic gram-negative rods Enterococci</td>
<td>Aerobic gram-negative rods Staphylococci</td>
</tr>
<tr>
<td><strong>Empiric antibiotic therapy</strong></td>
<td>Imipenem-cilastatin or meropenem or cefepime</td>
<td>Imipenem or meropenem or piperacillin-tazobactam ± aminoglycoside (consider amphotericin B)</td>
<td>Vancomycin plus cefepime</td>
<td>Vancomycin plus cefepime</td>
<td>Cefepime plus vancomycin</td>
</tr>
</tbody>
</table>

*Dosages for IV administration (normal renal function):
- Imipenem-cilastatin, 0.5 g q6h
- Meropenem, 1.0 g q8h
- Piperacillin-tazobactam, 3.375 g q4h or 4.5 g q6h
- Vancomycin, 15 mg/kg q12h (if meningitis, 25 mg/kg q12h)
- Cefepime, 1-2 g q8h
- Ciprofloxacin, 400 mg q12h; gatifloxacin, 400 mg qd; moxifloxacin, 400 mg qd
- Ceftriaxone, 2.0 g q24h
- Levofoxacin, 500 mg qd
Diseases and Disorders

- Vasopressors are indicated only when previous measures fail to correct the hypotension and PCWP has been raised to 15-18 mm Hg; norepinephrine should be titrated to raise the mean BP to ≥60 mm Hg.
- Drain any septic foci; necrotic bowel should be treated surgically.
- Intubation and mechanical ventilation if the arterial O₂ tension is <60 mm Hg w/FIO₂ >0.6 or RR >35 breaths/min.
- Alterations in adrenal function are common in pts w/critical illness, and steroid supplementation can improve survival in pts w/adrenal insufficiency associated w/illness. Corticosteroids (200-300 mg of hydrocortisone, or equivalent) daily IV for ≥100 h is beneficial in adults w/vasopressor-dependent septic shock (JAMA 301:2362-2375, 2009).
- Correct severe thrombocytopenia w/platelet concentrates.
- Correct depletion of coagulation factors w/FFP.
- Vasopressin acts as a peripheral vasoconstrictor and has been used in pts w/refractory vasodilatory shock; however, peripheral gangrene is a risk if volume resuscitation has not been accomplished.

### SEROTONIN SYNDROME (SS)

#### Definition
Group of sx resulting from ↑ activity of serotonin (5-hydroxytryptamine) in the CNS. It is a drug-induced disorder that is characterized by a ΔMS and alteration in neuromuscular activity and autonomic function.

#### Diagnosis
- Clonus w/hyperreflexia in the setting of recent (<5 wk) use of serotonergic agents
- Sx can be manifested within minutes to hours after a new psychopharmacologic treatment is started or after a second serotonergic drug is administered.
- Other pertinent findings include
  - Confusion, agitation, hypomania
  - Fever >58°C (100°F), tachycardia, and tachypnea
  - N/V, abd pain, and diaphoresis
  - Diarrhea, tremors, shivering, and seizures
  - Hyperreflexia and muscle rigidity

#### Etiology
- ↑ SSRI dose or addition of a serotonergic agent to the pt’s established regimen
- Drugs that ↑ serotonin release: amphetamines, cocaine, codeine, dextromethorphan, levodopa, fenfluramine, pentazocine, risperidone
- Drugs that ↓ serotonin reuptake: SSRIs, carbamazepine, cyclic antidepressants, trazodone, venlafaxine, meperidine, methadone
- Direct or indirect serotonin receptor agonists: buspirone, lithium, sumatriptan, mescaline and other phenylalkylamines

#### Treatment
- No specific antidote exists for SSRI OD.
- Useful meds to antagonize certain serotonin receptors are
  - Cyproheptadine 4-8 mg PO q1-4h until a therapeutic dose is achieved (max adult dose is 32 mg). It can also be administered in liquid form by NG tube (0.25 mg/kg/day divided into 3 equal doses).
  - Lorazepam 1 mg IV q30min: for muscle rigidity, myoclonus, and seizures
  - Propranolol also has some serotonin blocking activity.
- Ventricular dysrhythmias: Rx w/standard antidysrhythmic agents

#### Clinical Pearls
- Concomitant use of SSRI w/MAOI poses the greatest risk for development of SS.
- Triptans used for migraines may also precipitate SS when used in combination w/SSRIs and SNRIs.
- Diagnostic criteria: Hunter Serotonin Toxicity Criteria (sensitivity 84%, specificity 97%). Use of serotonergic drug and ≥1 of the following:
  - Spontaneous clonus
  - Inducible clonus + agitation or diaphoresis
• Ocular clonus + agitation or diaphoresis
• Tremor and hyperreflexia
• Temperature >38°C (100°F) + clonus or inducible clonus

343 SHORT BOWEL SYNDROME

Definition
Malabsorption syndrome that results from extensive small intestinal resection.

Diagnosis
■ Diarrhea and steatorrhea
■ Weight loss
■ Anemia related to iron or vitamin B₁₂ absorption
■ Bleeding diathesis related to vitamin K malabsorption
■ Osteoporosis/osteomalacia related to vitamin D and Ca malabsorption
■ Hyponatremia, hypokalemia
■ Hypovolemia
■ Other macronutrient or micronutrient deficiency states

Treatment
■ Pt w/extensive small bowel resection w/colectomy (<100 cm of jejunum): long-term TPN. Some pts can switch to oral intake after 1-2 yr of TPN. In jejunostomy pts, excessive fluid loss can be ↓ w/H₂ blockers, PPIs, or octreotide. Micronutrients are supplemented.
■ Pt w/extensive small bowel resection w/partial colectomy (usually pts w/Crohn’s disease): oral intake alone is possible in all pts w/100 cm of jejunum. In addition to vitamin B₁₂ deficiency, these pts often have diarrhea. Consider lactose malabsorption and bacterial overgrowth treatment w/lactose restriction and abx (tetracycline 250 mg tid or metronidazole 500 mg tid for 2 wk).

344 SICKLE CELL DISEASE

Definition
Hemoglobinopathy characterized by the production of Hgb S caused by substitution of the amino acid valine for glutamic acid in the sixth position of the γ-globin chain. When exposed to lower oxygen tension, RBCs assume a sickle shape, resulting in stasis of RBCs in capillaries. Painful crises are caused by ischemic tissue injury resulting from obstruction of blood flow produced by sickled erythrocytes.

Diagnosis
H&P
■ PE is variable, depending on the degree of anemia and presence of acute vaso-occlusive syndromes or neurologic, CV, GU, and musculoskeletal complications. Pain in adults w/sickle cell disease is the rule rather than the exception and is far more prevalent and severe than reported in older large-scale surveys.
■ There is no clinical laboratory finding that is pathognomonic of painful crisis of sickle cell disease. The dx of a painful episode is made solely on the basis of H&P.
■ Bones are the most common site of pain. Dactylitis, or hand-foot syndrome (acute, painful swelling of the hands and feet), is the first manifestation of sickle cell disease in many infants. Irritability and refusal to walk are other common sx. After infancy, musculoskeletal pain can be symmetric, asymmetric, or migratory, and it may or may not be associated w/swelling, low-grade fever, redness, or warmth.
■ In both children and adults, sickle vaso-occlusive episodes are difficult to distinguish from osteomyelitis, septic arthritis, synovitis, rheumatic fever, or gout.
■ When abd or visceral pain is present, care should be taken to exclude sequestration syndromes (spleen, liver) or the possibility of an acute condition such as appendicitis, pancreatitis, cholecystitis, UTI, PID, or malignant neoplasm.
■ Pneumonia develops during the course of 20% of painful events and can be manifested as chest and abd pain. In adults, chest pain may be a result...
of vaso-occlusion in the ribs and often precedes a pulmonary event. The lower back is also a frequent site of painful crisis in adults.

- The **acute chest syndrome** is manifested w/chest pain, fever, wheezing, tachypnea, and cough. CXR reveals pulmonary infiltrates. Common causes include infection (mycoplasma, chlamydia, viruses), infarction, and fat embolism.

- Musculoskeletal and skin abnormalities: leg ulcers (particularly on the malleoli) and limb-girdle deformities caused by avascular necrosis of the femoral and humeral heads

- Endocrine abnormalities: delayed sexual maturation and late physical maturation, especially evident in boys

- Neurologic abnormalities: seizures and ΔMS

- Infections: *Salmonella, Mycoplasma*, and *Streptococcus* are common.

- Severe splenomegaly secondary to sequestration often occurs in children before splenic atrophy.

**Labs**

- Hgb electrophoresis: confirms dx and can identify Hgb variants, such as fetal Hgb and Hgb A₂.

- CBC: anemia (resulting from chronic hemolysis), leukocytosis, and thrombocytosis are common.

- ↑ Bili and LDH

- Peripheral blood smear: sickle cells, target cells, poikilocytosis, hypochromia

- ↑ BUN and Cr: in pts w/progressive renal insufficiency

- U/A: hematuria, proteinuria

**Imaging**

- CXR

- Bone scan or MRI scan in suspected osteomyelitis

- CT or MRI of brain: in pts w/TIA, CVA, seizures, or ΔMS

- Transcranial Doppler study: in pts at risk for stroke

- Doppler echocardiography: r/o pulmonary HTN

**Treatment**

- Avoidance of conditions that may precipitate sickling crisis, such as hypoxia, infections, acidosis, and dehydration

- Maintain adequate hydration (PO or IV).

- Correct hypoxia.

- Ceph and azithromycin + incentive spirometry and bronchodilators in pts w/acute chest syndrome

- Pain relief during the vaso-occlusive crisis.

  - Narcotics (e.g., morphine 0.1 mg/kg IV q3–4h or 0.3 mg/kg PO q4h) should be given on a fixed schedule (not PRN for pain), w/rescue dosing for breakthrough pain as needed.

  - Except when contraindications exist, concomitant use of NSAIDs should be standard treatment.

  - When the pt shows signs of improvement, narcotic drugs should be tapered gradually to prevent withdrawal syndrome. It is advisable to observe the pt receiving oral pain relief medications for 12–24 hr before discharge from the hospital.

  - Analgesic medications should be used in combination w/psychological, behavioral, and physical modalities in the management of sickle cell disease.

- Avoid “routine” transfusions but consider early transfusions for pts at high risk for complications. Indications for transfusion: aplastic crises, severe hemolytic crises (particularly during third trimester of pregnancy), acute chest syndrome, and high risk of stroke.

- Hydroxyurea (15 mg/kg BW per day in pts w/nl CrCl) ↑ Hgb F levels and ↓ the incidence of vaso-occlusive complications. It is indicated for adults who have moderate to severe disease, typically those w/≥3 acute painful crises or episodes of the acute chest syndrome in the previous year.

- Replace folic acid (1 mg PO qd).
**Clinical Pearls**
- Exchange transfusions may be necessary for pts w/acute neurologic signs, in aplastic crisis, or undergoing surgery.
- Allogeneic SCT can be curative in young pts w/symptomatic sickle cell disease; however, the death rate from the procedure is nearly 10%.
- PCN V 125 mg PO bid should be administered by age 2 mo and ↑ to 250 mg bid by age 3 yr. PCN prophylaxis can be discontinued after age 5 yr except in children who have had splenectomy.

**345 SICK SINUS SYNDROME (BRADYCARDIA-TACHYCARDIA SYNDROME)**

**Definition**
Group of cardiac rhythm disturbances characterized by abnormalities of the sinus node, including (1) sinus bradycardia, (2) sinus arrest or exit block, (3) combinations of sinoatrial or AV conduction defects, and (4) supraventricular tachyarrhythmias. These abnormalities may coexist in a single pt so that a pt may have episodes of bradycardia and episodes of tachycardia.

**Diagnosis**

**H&P**
- Clinical presentation: lightheadedness, dizziness, syncope, palpitation

**Imaging**
- ECG (Fig. 3-44)
- Ambulatory cardiac rhythm monitoring
- 24-hr ambulatory ECG (Holter)
- Event recorder

![Supraventricular tachycardia](image)

**Figure 3-44.** Brady-tachy (sick sinus) syndrome. This rhythm strip shows a narrow-complex tachycardia (probably atrial flutter) followed by a sinus pause, an AV junctional escape beat (J), and then sinus rhythm.

**Etiology**
- Fibrosis or fatty infiltration involving the sinus node, the AV node, or the His bundle or its branches
- In addition, inflammatory or degenerative changes of the nerves and ganglia surrounding the sinus nodes and other sclerodegenerative changes may be found.

**Treatment**
- Permanent pacemaker placement if sx are present
- The drug treatment of the tachycardia may worsen or bring out the bradycardia and become the reason for pacemaker requirement.

**346 SINUSOIDAL OBSTRUCTION SYNDROME (VENO-OCCCLUSIVE DISEASE)**

**Definition**
In situ thrombosis w/occlusion of sinusoids and hepatic venules.

**Diagnosis**

**H&P**
- Jaundice, RUQ pain, ascites, hepatomegaly

**Labs**
- ↑ Bili, INR, LFTs
- Liver bx will confirm dx.
**SJÖGREN’S SYNDROME (SS)**

**Definition**
Autoimmune disorder characterized by lymphocytic and plasma cell infiltration and destruction of salivary and lacrimal glands w/subsequent diminished lacrimal and salivary gland secretions.

**Primary**: dry mouth (xerostomia) and dry eyes (xerophthalmia) develop as isolated entities.

**Secondary**: associated w/other disorders

**Diagnosis**

**Primary**
- Sx and objective signs of ocular dryness:
  - Schirmer’s test: <8 mm wetting per 5 min
  - Positive rose bengal or fluorescein staining of cornea and conjunctiva to demonstrate keratoconjunctivitis sicca
- Sx and objective signs of dry mouth:
  - ↓ Parotid flow by Lashley cups or other methods
  - Abnl bx result of minor salivary gland (focus score >2 based on average of 4 assessable lobules)
- Evidence of systemic autoimmune disorder:
  - ↑ Titer of RF >1:320
  - ↑ Titer of ANA >1:320
  - Presence of anti-SSA (Ro) or anti-SSB (La) Abs

**Secondary**
Characteristic signs and sx of SS:
- Dry mouth w/dry lips (cheilosis), erythema of tongue and other mucosal surfaces, carious teeth
- Dry eyes (conjunctival injection, ↓ luster, and irregularity of the corneal light reflex)
- Salivary gland enlargement and dysfunction w/subsequent difficulty in chewing and swallowing food and in speaking w/o frequent water intake
- Purpura (nonthrombocytopenic, hyperglobulinemic, vasculitic)
- Evidence of associated conditions (e.g., RA or other connective disease, lymphoma, hypothyroidism, COPD, trigeminal neuropathy, chronic liver disease, polymyopathy)

**Labs**
- + ANA (>60% of pts) w/ anti-SSA and anti-SSB
- ↑ ESR, anemia (normochromic, normocytic), abnl LFTs, ↑ serum β₂-microglobulin levels, + RF.
- A definite dx SS can be made w/a salivary gland bx.

**Treatment**
- Adequate fluid replacement
- Proper oral hygiene to ↓ the incidence of caries
- Use artificial tears frequently.
- Pilocarpine 5 mg PO qid: useful to improve dryness. A cyclosporine 0.05% ophthalmic emulsion (Restasis) may also be useful for dry eyes. Recommended dose is 1 drop bid in both eyes.
- Cevimeline: cholinergic agent w/muscarinic agonist activity; 30 mg PO tid is effective for the treatment of dry mouth.
- Interferon alfa, 150 IU tid for 12 wk
348 SMALL BOWEL OBSTRUCTION

**Diagnosis**

**H&P**
- Colicky abd pain, N/V, abd distention
- Failure to pass gas and feces
- Tachycardia, hypotension, dehydration, fever (if strangulation is present)
- Distended abd, tenderness w/ or w/o a palpable mass, hyperactive bowel sounds initially followed by ↓ bowel sounds late in obstruction

**Labs**
- Lytes, BUN, Cr, ALT, amylase: generally not helpful

**Imaging**
- Plain abd films: dilated loops of small intestine w/o evidence of colonic distention, air-fluid levels
- CT: sensitive for dx complete or high-grade obstruction (less sensitive for partial obstruction). It can also identify cause of obstruction (e.g., abscess, neoplasm).
- Barium studies: enteroclysis (oral insertion of a tube into the duodenum and instillation of air and barium) may be useful for low-grade or intermittent obstruction.

**Etiology**
- Most commonly due to adhesions from prior surgery (60%)
- Hernias (25%)
- Malignant tumors (15%)

**Treatment**
- IV fluid resuscitation
- NG suction w/a Levin tube to empty stomach
- Prophylactic broad-spectrum abx
- Operative management

349 SPINAL CORD COMPRESSION

**Definition**
Spinal cord compression is the neurologic loss of spine function. Lesions may be complete or incomplete and develop gradually or acutely. Incomplete lesions often are manifested as distinct syndromes, as follows:
- Central cord syndrome
- Anterior cord syndrome
- Brown-Séquard syndrome
- Conus medullaris syndrome
- Cauda equina syndrome

**Diagnosis**

**H&P**
- Clinical features reflect the amount of spinal cord involvement:
  - Motor loss and sensory abnormalities
  - + Babinski
  - Clonus
  - Gradual compression: manifested by progressive difficulty walking, clonus w/weight bearing, and involuntary spasm; development of sensory sx; bladder dysfunction (late)
- **Central cord syndrome**: variable quadriaparesis, w/UEs more severely involved than the LEs; some sensory sparing
- **Anterior cord syndrome**: motor, pain, and temperature loss below the lesion
- **Brown-Séquard syndrome:**
  - Caused by injury to either half of the spinal cord and resulting in the loss of motor function, position, vibration, and light touch on the affected side
  - Pain and temperature sense loss on the opposite side
- **Conus medullaris syndrome**: variable motor loss in the LEs w/loss of bowel and bladder function
- **Cauda equina syndrome**: typical low back pain, weakness in both LEs, saddle anesthesia, and loss of voluntary bladder and bowel control


**Imaging**
- MRI

**Etiology**
- Trauma
- Tumor
- Infection
- Inflammatory processes
- Degenerative disk conditions w/spinal stenosis
- Acute disk herniation
- Cystic abnormalities

**Treatment**
- Urgent surgical decompression

**Clinical Pearl**

Important indicators of prognosis:
- The greater the distal motor and sensory sparing, the greater the expected recovery.
- When a plateau of recovery is reached, no further improvement is expected.
- The quicker the recovery, the greater the recovery.

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**STATUS ASTHMATICUS**

**Definition**
Severe continuous bronchospasm.

**Diagnosis**

**H&P**
- Progressively worsening dyspnea, cough, tachypnea, chest tightness, and wheezing during a period of hours to days
- Pt sitting forward, diaphoretic, may be unable to speak because of severe dyspnea
- PE
  - Tachycardia and tachypnea
  - Use of accessory respiratory muscles
  - *Pulsus paradoxus* (inspiratory ↓ in systolic BP >10 mm Hg)
- Wheezing: the absence of wheezing (silent chest) or ↓ wheezing can indicate worsening obstruction
- ΔMS: due to hypoxia and hypercapnia and constitute an indication for urgent intubation
- An important sign of impending respiratory crisis is paradoxical abd and diaphragmatic movement on inspiration (detected by palpation over the upper part of the abd in a semirecumbent position); it indicates diaphragmatic fatigue.
- Objective measurements of severe airflow obstruction are peak expiratory flow <50% and FEV₁ <50%.
- The following VS are indicative of severe asthma:
  - Pulsus paradoxus >18 mm Hg
  - RR >30 breaths/min
  - Tachycardia w/HR >120 bpm

**Labs**
- ABGs can be used in staging the severity of the asthmatic attack.
  - Mild: ↓ PaO₂ and PaCO₂, ↑ pH
  - Moderate: ↓ PaO₂, nl PaCO₂, nl pH
  - Severe: markedly ↓ PaO₂, ↑ PaCO₂, and ↓ pH
  - Note: a nl or ↑ PaCO₂ should be interpreted as a sign of impending respiratory failure.
- CBC: leukocytosis w/left shift may indicate coexistence of bacterial infection (e.g., pneumonia).
- Sputum: eosinophils, Charcot-Leyden crystals, polymorphonuclear leukocytes, and bacteria may be found on Gram stain in pts w/pneumonia.

**Imaging**
- CXR: generally shows only evidence of thoracic hyperinflation (e.g., flattening of diaphragm, ↑ volume of the retrosternal air space). It is useful to r/o pneumonia, atelecstasis, or pneumothorax as complicating conditions.
Diseases
between discrete or ≥min, seizures

STATUS EPILEPTICUS
Diagnosis
Continuous seizure activity lasting ≥5 min, or ≥2 discrete seizures between which there is incomplete recovery of consciousness.

Treatment
Supplemental O₂: by nasal cannula (each L/min of flow generally adds 2% to the Fio₂) or w/Ventimask (24%, 28%, 31%, 35%, 40%, and 50%)
- It is generally started at 2–4 L/min by nasal cannula or Ventimask at 40% Fio₂.
- Further adjustments are made according to pulse oximetry or ABGs.
- Goal is to maintain oxygen saturation >90%.

Bronchodilators: various agents and modalities are available. Inhaled bronchodilators are preferred when they can be administered quickly.
- Parenteral administration of sympathomimetics (e.g., SC epinephrine) when necessary should be accompanied by ECG monitoring. Albuterol: 0.5-1 mL (2.5-5 mg) in 3 mL of saline solution tid or qid by nebulizer is effective.
- Other useful medications are levalbuterol nebulizer solution (0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL) and ipratropium nebulizer solution (0.25 mg/mL [0.025%]).

Corticosteroids: methylprednisolone, 0.5-1 mg/kg IV loading dose, then q6h PRN; higher doses may be necessary in selected pts (particularly those receiving steroids at home); steroids given by inhalation (e.g., beclomethasone, two inhalations qid; max 20 inhalations per day) are also useful in controlling bronchospasm and tapering oral steroids and should be used in all pts w/severe asthma.

- IV hydration
- IV abx are indicated when there is suspicion of bacterial infection (e.g., infiltrate on CXR, fever, or significant leukocytosis).
- Intubation and mechanical ventilation are indicated when the preceding measures fail to produce significant improvement.
- IV Mg sulfate supplementation in pts w/low or borderline-low Mg levels may improve acute bronchospasm and airflow. When the use of Mg is necessary, a 20-min infusion of 1.2 g of Mg sulfate is generally effective.

351 STATUS EPILEPTICUS
Definition
Continuous seizure activity lasting ≥5 min, or ≥2 discrete seizures between which there is incomplete recovery of consciousness.

Diagnosis
- In convulsive status epilepticus, pts are unresponsive and have obvious tonic, clonic, or tonic-clonic movements of the extremities.
- Presentation of pts in nonconvulsive status epilepticus varies from complete unresponsiveness w/little or no observable motor activity to confusion w/ or w/o repetitive behaviors or automatisms.

Management
- Oxygen by nasal cannula or non-rebreathing mask
- Maintain BP, monitor ECG.
- Obtain IV access. Draw ABGs, electrolyte, glucose, BUN, Cr, Ca, Mg, toxicology screen, and anticonvulsant levels (in pts receiving anticonvulsants).
- Endotracheal intubation for refractory status epilepticus or signs of respiratory distress
  - 0-5 min: thiamine 100 mg IV and glucose 50 mg D₅₀ by IV push (2 mL/kg D₅₀ in children) unless hyperglycemic
  - 5-10 min: lorazepam 2 mg/min IV up to 0.1 mg/kg
  - >10 min: fosphenytoin 20 mg/kg, fosphenytoin equivalents (PE) IV up to 150 mg/min (if not available, use phenytoin 20 mg/kg IV at up to 50 mg/min); can be followed by an additional 5-10 mg/kg PE IV if seizures persist
  - >45 min (refractory status epilepticus): load phenobarbital 20 mg/kg IV or induce general anesthesia w/midazolam, propofol, or pentobarbital by continuous IV drip
EEG should be obtained to evaluate for nonconvulsive status epilepticus in any pt who does not regain consciousness within 1-2 hr of cessation of convulsive activity and for all pts requiring general anesthesia for seizure control.

**Clinical Pearl**
- If seizure activity persists >60 min, consider institution of general anesthesia w/isoflurane and neuromuscular blockade. Continuous seizures at this point are often due to metabolic disturbances (e.g., hyponatremia, hypocalcemia) or serious intracranial lesions (e.g., neoplasm, abscess), and the seizures will not stop unless the underlying disorder is corrected.

### 352 STEVENS-JOHNSON SYNDROME (SJS)

**Definition**
Severe vesiculobullous form of erythema multiforme affecting skin, mouth, eyes, and genitalia. Drugs (e.g., phenytoin, PCNs, phenobarbital, sulfonamides) are the most common cause. URIs (e.g., *Mycoplasma pneumoniae*) and HSV infections have also been implicated in SJS.

**Diagnosis**
- The cutaneous eruption is generally preceded by vague, nonspecific sx of low-grade fever and fatigue occurring 1-14 days before the skin lesions. Cough is often present. Fever may be high during the active stages.
- Bullae generally occur on the conjunctiva, mucous membranes of the mouth, nares, and genital regions.
- Ulcerative stomatitis results in hemorrhagic crusting.
- Flat, atypical target lesions or purpuric maculae may be distributed on the trunk or be widespread.
- Skin bx is reserved for when classic lesions are absent and dx is uncertain.

**Treatment**
- Withdrawal of any potential drug precipitants
- Rx of associated conditions, (e.g., acyclovir for HSV infection, erythromycin for *Mycoplasma* infection)
- Antihistamines for pruritus
- Rx for the cutaneous blisters w/cool, wet Burow’s compresses
- Relief of oral sx by frequent rinsing w/lidocaine (Xylocaine Viscous)
- Liquid or soft diet w/plenty of fluids to ensure proper hydration
- Corticosteroids: use remains controversial; when used, prednisone 20-30 mg bid until new lesions no longer appear, then rapidly tapered
- Topical steroids: may use to treat papules and plaques; however, should not be applied to eroded areas
- Vitamin A: may be used for lacrimal hyposcretion

**Clinical Pearls**
- Prognosis varies w/severity of disease. It is generally good in pts w/limited disease; however, mortality may approach 10% in pts w/extensive involvement.
- Oral lesions may continue for several months.
- Scarring and corneal abnormalities may occur in 20% of pts.

### 353 STROKE, INTRACEREBRAL HEMORRHAGE

**Definition**
Neurologic deficit secondary to intracerebral hemorrhage.

**Diagnosis**

**H&P**
- Neurologic deficits vary w/the area involved (Table 3-40).
- Signs of ↑ ICP (e.g., bradycardia, ↓ RR, third nerve palsy)

**Imaging**
- CT scan of the head: area of hemorrhagic infarct appears as a zone of ↑ density.

**Etiology**
- HTN (50%-60% of cases), cerebral amyloid angiopathy (10%), hemorrhagic infarcts (10%), use of anticoagulants and fibrinolytic agents (10%), brain tumors (5%), vascular malformations (5%)
Treatment

- Pts should be at bed rest w/head of the bed elevated 30 degrees.
- Pneumatic compression devices for LEs are necessary to prevent DVT.
- All fluids should be given in NS if possible to maintain serum sodium and osmolality. Hypotonic fluids may worsen cerebral edema. Total IV fluid intake should be generally limited to 1.5 L/day.
- Supportive measures: urinary catheter insertion; A-line (if BP management is needed); intubation of pts w/depressed level of consciousness and inability to protect airway from aspiration; rotation schedule to prevent decubitus ulcers
- Control of severe HTN: lower BP may ↓ cerebral edema but risks promoting border zone ischemia. As a very rough guide, BP reduction should be considered if systolic BP is >180 mm Hg or diastolic BP is >100 mm Hg. If the pre-hemorrhage BP is known, MAP should not be lowered >25% from baseline \[\text{MAP} = \text{diastolic BP} + \text{pulse pressure/3}\]. IV nitroprusside is a useful agent for BP control because it is effective, has rapid onset of action, and can be easily titrated.
- Management of ↑ ICP can be achieved w/mannitol. Intubation and ventilation of pts w/↑ ICP are recommended to prevent hypoxia and hypercapnia (both powerful stimuli for cerebral vasodilation).
- Surgical evacuation of hematomas in the following situations:
  - Noncomatose pts w/cerebellar hemorrhage
  - Pts w/surgically accessible cerebral hematomas that produce progressive signs of temporal lobe herniation
  - The size of the hematoma and the level of consciousness are of prognostic significance; awake pts w/small hematoma (<3 cm) often

<table>
<thead>
<tr>
<th>Location of Intracerebral Hemorrhage</th>
<th>Common Neurologic Signs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Putamen</td>
<td>Both eyes deviate conjugately to the side of the lesion (away from hemiparesis) Pupils normal in size and react normally Contralateral hemiplegia present Hemisensory defect noted</td>
<td><img src="image" alt="Left putaminal hemorrhage" /></td>
</tr>
<tr>
<td>Thalamus</td>
<td>Both eyes deviate downward and look at the nose Impairment of vertical eye movements present Pupils small (approximately 2 mm) and nonreactive Contralateral hemisensory loss present</td>
<td><img src="image" alt="Thalamic hemorrhage" /></td>
</tr>
<tr>
<td>Pons</td>
<td>Both eyes in midposition No doll’s-eye movements Pupils are pinpoint but reactive (use magnifying glass) Coma is common Flaccid quadriplegia noted</td>
<td><img src="image" alt="Pontine hemorrhage" /></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Ipsilateral paresis of conjugate gaze (inability to look toward side of lesion) Pupils normal in size and react normally Inability to stand or to walk Vertigo and dysarthria present</td>
<td><img src="image" alt="Cerebellar hemorrhage" /></td>
</tr>
</tbody>
</table>

**TABLE 3-40** Localizing Signs in Patients with Intracerebral Hemorrhage

- Putamen: Both eyes deviate conjugately to the side of the lesion (away from hemiparesis) Pupils normal in size and react normally Contralateral hemiplegia present Hemisensory defect noted
- Thalamus: Both eyes deviate downward and look at the nose Impairment of vertical eye movements present Pupils small (approximately 2 mm) and nonreactive Contralateral hemisensory loss present
- Pons: Both eyes in midposition No doll’s-eye movements Pupils are pinpoint but reactive (use magnifying glass) Coma is common Flaccid quadriplegia noted
- Cerebellum: Ipsilateral paresis of conjugate gaze (inability to look toward side of lesion) Pupils normal in size and react normally Inability to stand or to walk Vertigo and dysarthria present
recover w/o surgery, whereas comatose pts w/hemorrhages >6 cm do poorly regardless of medical or surgical management.

### STROKE, ISCHEMIC

#### Definition
Rapid onset of neurologic deficit involving a certain vascular territory secondary to thrombosis or embolism (Table 3-41).

#### Diagnosis

- **H&P**
  - Clinical presentation varies w/the cerebral vessel involved (Table 3-42).

- **Imaging**
  - CT of brain: area of ↓ density; initial CT scan may be normal, and infarct may not be evident for 2-3 days after the infarct.

#### Treatment

- **Thrombolysis:** pts who present within 3 hr of ischemic stroke onset and who meet specific inclusion and exclusion criteria should be considered for IV thrombolytic Rx.

- **Acute anticoagulation w/heparin, low-molecular-weight heparin, and heparinoids** provides no benefit while ↑ hemorrhagic complications in pts w/cardioembolic stroke, lacunar stroke, or stroke of unknown etiology.

- **Antiplatelet agents** for secondary prevention of atherothrombotic strokes include ASA, clopidogrel, and combination of ASA and dipyridamole.

---

#### TABLE 3-41 Characteristics of Thrombosis and Embolism

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thrombosis</th>
<th>Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sx</td>
<td>Progression of sx during hours to days</td>
<td>Very rapid (seconds)</td>
</tr>
<tr>
<td>Hx of previous TIA</td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Time of presentation</td>
<td>Often during night hours while the pt is sleeping Classically, the pt awakens w/a slight neurologic deficit that gradually progresses in a stepwise fashion</td>
<td>Pt is usually awake and involved in some type of activity</td>
</tr>
<tr>
<td>Predisposing factors</td>
<td>Atherosclerosis, HTN, diabetes, arteritis, vasculitis, hypotension, trauma to head and neck</td>
<td>AF, mitral stenosis and regurgitation, endocarditis, mitral valve prolapse</td>
</tr>
</tbody>
</table>

#### TABLE 3-42 Selected Stroke Syndromes

<table>
<thead>
<tr>
<th>Artery Involved</th>
<th>Neurologic Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle cerebral artery</td>
<td>Hemiplegia (UEs and face are usually more involved than LEs) Hemianesthesia (hemisensory loss) Hemianopia (homonymous) Aphasia (if dominant hemisphere is involved)</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>Hemiplegia (LEs more involved than UEs and face) Primitive reflexes (e.g., grasp and suck) Urinary incontinence</td>
</tr>
<tr>
<td>Vertebral and basilar arteries</td>
<td>Ipsilateral cranial nerve findings, cerebellar findings Contralateral (or bilateral) sensory or motor deficits</td>
</tr>
<tr>
<td>Deep penetrating branches of major cerebral arteries (lacunar infarction)</td>
<td>Usually seen in elderly HTN pts and diabetics Four characteristic syndromes are possible: 1. Pure motor hemiplegia (66%) 2. Dysarthria—clumsy hand syndrome (20%) 3. Pure sensory stroke (10%) 4. Ataxic hemiplegia syndrome w/pyramidal tract signs</td>
</tr>
</tbody>
</table>
Lowering of systemic BP in pts w/acute cerebral infarction is dangerous because it may produce clinical deterioration (secondary to spontaneous fluctuation in BP and impaired cerebral autoregulation) unless one of the following conditions is present:
- Diastolic pressure \( \geq 120 \) mm Hg or systolic pressure \( >230 \) mm Hg
- Hypertensive encephalopathy is present.
- Vital organs (heart, kidney) are compromised.
- There is cerebral ischemia secondary to aortic dissection.
- Most pts w/acute cerebral infarction have ↑ BP, which generally returns to baseline within 48 hr w/o additional treatment.

**Clinical Pearl**
- Carotid endarterectomy may be indicated after atherothrombotic stroke for pts whose surgery can be delayed at least 1 mo and who have minor residual deficits associated w/high-grade ipsilateral stenosis, or large ulcerative lesions, and have a low to medium surgical risk.

**355 SUBARACHNOID HEMORRHAGE (SAH)**

**Definition**
Presence of active bleeding into the subarachnoid space.

**Diagnosis**

**H&P**
- Abrupt onset of severe occipital or generalized headache that radiates into the posterior neck region and is worsened by neck and head movements; often described as “the worst headache” of his or her life
- Restlessness, vomiting, diminished level of consciousness, syncope
- Focal neurologic signs usually are absent.
- Level of consciousness varies from nl to deeply comatose.
- Fever and nuchal rigidity are present or usually develop within 24 hr.
- Fundi may show papilledema or retinal hemorrhage.
- Cranial nerve abnormalities may be noted (e.g., pupillary dilation secondary to oculomotor nerve dysfunction).
- HTN may be present and can lead to an incorrect dx of primary hypertensive emergency.
- Tachycardia and irregular heartbeat may be present (up to 91% of pts w/SAH have cardiac arrhythmias).

**Imaging**
- CT of brain: fresh hemorrhage produces an area of ↑ density; scan may be nl if done >48 hr after the SAH or if the hemorrhage is small. Very thin cuts (3 mm in thickness) through the base of the brain are recommended because thicker cuts (10 mm) may miss small collections of blood. MRI has a lower index of accuracy than that of CT in SAH.

**Etiology**
- Ruptured congenital aneurysm or AVM

**Treatment**
- Management of SAH varies w/the pt’s clinical status and the location and surgical accessibility of the aneurysm.
- Medical management:
  - Bed rest w/cardiac monitoring (frequent arrhythmias)
  - Control of headache w/acetaminophen and codeine
  - Avoidance of all forms of straining (stool softeners and mild laxatives indicated to prevent constipation)
  - Stress ulcer prophylaxis (e.g., IV H₂ blockers, PPIs, or sucralfate 1 g in 20 mL H₂O by NG tube tid) in pts on mechanical ventilation or w/prior h/o gastric ulcers
  - ↓ Cerebral edema w/mannitol
  - Nimodipine for cerebral blood vessel spasm. It ↓ the incidence of permanent neurologic damage and death; Rx should be initiated within 96 hr of the onset of SAH; dosage is 60 mg q4h for 21 days; it may be administered by NG tube; ↓ dose in pts w/liver disease.
- Surgical management (clipping vs. coiling): the indications depend on the size of the aneurysm, the pt’s age and clinical condition, and the
experience of the neurosurgeon. Endovascular coiling w/a platinum coil device is also effective in enabling endovascular occlusion of intracranial aneurysms and ↓ risk for further rupture w/o craniotomy.

**Clinical Pearl**
- Rate of rebleeding for cerebral AVMs in pts w/SAH is 6% in the first 6 mo; thereafter, it is 4%/year, a rate identical to the yearly risk of a first hemorrhage in pts w/AVMs that have never bled. Therefore, surgery or endovascular coiling to prevent rebleeding or the initial bleed is much more desirable in a younger pt.

### 356 SUBCLAVIAN STEAL SYNDROME

**Definition**
Oclusion or severe stenosis of the proximal subclavian artery leading to ↓ antegrade flow or retrograde flow in the ipsilateral vertebral artery and neurologic sx referable to the posterior circulation.

**Diagnosis**
**H&P**
- UE ischemic sx: fatigue, exercise-related aching, coolness, numbness of the involved UE
- Neurologic sx occur in 25% of pts w/known unilateral subclavian steal. These include brief spells of vertigo, diplopia, unsteady gait. Spells are only occasionally provoked by exercising the ischemic UE (classic subclavian steal). Left subclavian steal is more common than right, but the right is more serious.
- Physical findings: delayed and smaller volume pulse (wrist or antecubital) in the affected UE, ↓ BP in the affected UE, supraclavicular bruit

**NOTE:** Inflation of BP cuff will ↑ the bruit if it originates from a vertebral artery stenosis and ↓ the bruit if it originates from a subclavian artery stenosis.

**Imaging**
- Doppler sonography of the vertebral, subclavian, and innominate arteries
- Arteriography

**Etiology**
- Atherosclerosis
- Arteritis (Takayasu’s disease and temporal arteritis)
- Embolism to the subclavian or innominate artery
- Cervical rib
- Chronic use of a crutch
- Occupational (baseball pitchers and cricket bowlers)

**Treatment**
- In most pts, the disease is benign and requires no treatment other than atherosclerosis risk factor modification and ASA. Sx tend to improve over time as collateral circulation develops.
- Vascular surgical reconstruction requires a thoracotomy; it may be indicated in innominate artery stenosis or when UE ischemia is incapacitating.

### 357 SUBDURAL HEMATOMA

**Definition**
Bleeding into the subdural space, caused by rupture of bridging veins between the brain and venous sinuses.

**Diagnosis**
**H&P**
- Vague headache, often worse in morning than evening
- Some apathy, confusion, and clouding of consciousness is common, although frank coma may complicate late cases. Chronic subdural hematomas may cause a dementia picture.
- Neurologic sx may be transient, simulating TIA.
- Almost any sign of cortical dysfunction may occur, including hemiparesis, sensory deficits, and language abnormalities, depending on which part of the cortex is compressed by the hematoma.
- New-onset seizures should raise the index of suspicion.
**SVC SYNDROME**

**Definition**
Set of sx that results when a mediastinal mass compresses the SVC or the veins that drain into it. The pathophysiologic mechanism of the syndrome involves the ↑ pressure in the venous system draining into the SVC, producing edema of the head, neck, and UEs. Sx develop during a period of 2 wk in 30% of pts.

**Diagnosis**

**H&P**
- Clinical presentation: dyspnea, chest pain, cough, dysphagia, syncope
- PE: chest wall vein distention, neck vein distention, facial edema, UE swelling, cyanosis

**Imaging**
- CXR
- Venography: warranted only when an intervention (e.g., stent or surgery) is planned
- Chest CT scan or MRI

**Etiology**
- Lung cancer (80% of all cases, of which half are small cell lung cancer)
- Lymphoma (15%)
- TB
- Goiter
- Aortic aneurysm (arteriosclerotic or syphilitic)
- SVC thrombosis
  - Primary: associated w/a central venous catheter
  - Secondary: as a complication of SVC syndrome associated w/one of the above-mentioned causes

**Treatment**
- Management is guided by severity of sx and the underlying etiology.
- Emergency RT is indicated in critical situations, such as respiratory failure or CNS signs associated w/ICP.
- Treatment of the underlying malignant disease:
  - Radiotherapy: the majority of tumors causing the SVC syndrome are sensitive to radiotherapy
  - Systemic/chemotherapy
  - Anticoagulant or fibrinolytic therapy in pts who do not respond to cancer treatment within a week or if an obstructing thrombus has been documented
  - Loop diuretics are often used, but their effect is limited.
  - Upright positioning and fluid restriction until collateral channels develop and allow clinical regression are useful modalities for SVC syndrome secondary to benign disease.
Diseases

Steroids (dexamethasone 4 mg q6h): may be useful in reducing the tumor burden in lymphoma and thymoma.

Percutaneous self-expandable stents that can be placed under local anesthesia w/radiologic manipulation are useful in the treatment of SVC syndrome to bypass the obstruction, especially in cases associated w/malignant tumors.

Surgical bypass grafting is infrequently used to treat SVC syndrome.

SYNCOPE

Definition
Temporary loss of consciousness resulting from an acute global reduction in cerebral blood flow.

Diagnosis

Hx
- Sudden loss of consciousness: consider cardiac arrhythmias, vertebrobasilar TIA
- Gradual loss of consciousness: consider orthostatic hypotension, vasodepressor syncope, hypoglycemia
- Pt’s activity at the time of syncope:
  • Micturition, coughing, defecation: syncope caused by ↓ venous return
  • Turning his head while shaving: carotid sinus syndrome
  • Physical exertion in pt w/murmur: AS
  • Arm exercise: subclavian steal syndrome
  • Assuming an upright position: orthostatic hypotension
- Associated events:
  • Chest pain: MI, PE
  • Palpitations: dysrhythmias
  • H/o aura, incontinence during episode, and transient confusion after “syncope”: seizure disorder
  • Psychic stress: consider vasovagal syncope
  • Current meds, particularly anti-HTN drugs: hypotension due to meds

PE
- BP: if low, consider orthostatic hypotension. If unequal in both arms (difference >20 mm Hg), consider subclavian steal or dissecting aneurysm. BP and HR should be recorded in the supine, sitting, and standing positions.
- Pulse: if pt has tachycardia, bradycardia, or irregular rhythm, consider dysrhythmia.
- Mental status: if pt is confused after the syncopal episode, consider postictal state.
- Heart: if murmurs are present, suggestive of AS or HOCM, consider syncope secondary to LV outflow obstruction; if JVD and distant heart sounds are present, consider cardiac tamponade.
- Carotid sinus pressure can be dx if it reproduces sx and other causes are excluded. A pause ≥3 sec or a systolic BP drop >50 mm Hg w/o sx or <50 mm Hg w/sx when sinus pressure is applied separately on each side for ≤5 sec is considered abnl; this test should be avoided in pts w/carotid bruits or cerebrovascular disease. ECG monitoring, IV access, and bedside atropine should be available when carotid sinus pressure is applied.

Initial Diagnostic Tests (Fig. 3-45)
- Routine blood tests rarely yield diagnostically useful information and should be done only when they are specifically suggested by the results of H&P. The following tests should be considered:
  • CBC: r/o anemia, infection
  • Electrolytes, BUN, Cr, Mg, and Ca: r/o electrolyte abnormalities, hypomagnesemia, and hypocalcemia; evaluate fluid status
  • ECG: r/o arrhythmias; may be diagnostic in 5%-10% of pts
  • CXR: evaluate cardiac size, lung fields
  • ABGs: r/o PE, hyperventilation
  • Pregnancy test in women of childbearing age
Syncope

- Carotid sinus massage
- Detailed H&P
- ECG, labs
- Suspected seizure

Diagnostic (e.g., vasovagal syncope, orthostatic hypotension)

- Suspected CNS
- Suspected cardiac

- Carotid Doppler, CT of head, EEG
- Echocardiography
- 24-hr Holter monitor
- Exercise treadmill test
- EPS studies

Negative

Tilt-table testing

**FIGURE 3-45.** Diagnostic algorithm for syncope.

**Tilt table testing**
- Useful to support the dx of neurocardiogenic syncope and to identify pts w/prominent bradycardic response who may benefit from a permanent pacemaker.
- Indicated in pts w/recurrent episodes of unexplained syncope. Pts >50 yr should have stress testing before undergoing tilt table testing.

**Additional diagnostic tests may be indicated, depending on H&P.**
- If arrhythmias are suspected, 24-hr Holter monitor and admission to a telemetry unit are appropriate; in general, Holter monitoring is rarely useful, revealing a cause of syncope in <3% of cases. Loop recorders that can be activated after a syncopal event and retrieve information about the cardiac rhythm during the preceding 4 min have added considerable diagnostic yield in pts w/unexplained syncope.
- Echocardiography: indicated in pts w/heart murmur to r/o AS, HOCM, or atrial myxoma
- CT of brain and EEG: when seizure disorder is suspected
- CT of chest: when PE is suspected
- Cardiac isoenzymes or troponin in pt w/h/o chest pain before syncopal episode
- Blood and urine toxicology when toxicity or drug abuse is suspected

**Etiology**
- **Vasovagal (vasodepressor)**
  - Psychophysiological (panic disorders, hysteria)
  - Visceral reflex
  - Carotid sinus
  - Glossopharyngeal neuralgia
  - ↓ of venous return resulting from Valsalva maneuver, cough, defecation, or micturition
- **Orthostatic hypotension**
  - Hypovolemia
  - Hypotensive drugs
  - Neurogenic, idiopathic
  - Pheochromocytoma
  - Systemic mastocytosis
- **Cardiac**
  - ↓ CO
• LV outflow obstruction: AS, HOCM
• Obstruction to pulmonary flow (PE, pulmonic stenosis, PPH)
• MI w/pump failure
• Cardiac tamponade
• Mitral stenosis
• Dysrhythmias or asystole
• Extreme tachycardia (>160-180 bpm)
• Severe bradycardia (<30-40 bpm)
• SSS
• AV block (second or third degree)
• VT or VF
• LQTS

Cerebrovascular
• TIA, spasm
• Subclavian steal
• Basilar migraine
• Colloid cyst of third ventricle

Other causes
• Mechanical ↓ of venous return (atrial myxoma, ball-valve thrombus)
• Not related to ↓ blood flow: hypoxia, hypoglycemia, anemia, hyperventilation, seizure disorder, drug or alcohol abuse

Treatment
• Varies w/etiology of syncope

Prognosis
• Varies w/the age of the pt and the cause of the syncope
• Benign prognosis (low 1-year morbidity and mortality) in pts:
  • Aged <30 yr and having noncardiac syncope
  • Aged ≤70 yr and having vasovagal or psychogenic syncope
• Poor prognosis (high morbidity and mortality) in pts w/cardiac syncope.
  Pts w/syncope of unknown cause are also at ↑ risk for death from any cause.
• Pts w/≥3 of the following risk factors have a >30% 1-yr mortality risk: abnl ECG, h/o ventricular arrhythmias, h/o CHF, age >45 yr.

SYNDROME OF INAPPROPRIATE ANTI DIURESIS (SIAD; SYNDROME OF INAPPROPRIATE ANTI DIURETIC HORMONE, SIADH)

Definition
Syndrome characterized by excessive secretion of ADH in absence of nl osmotic or physiologic stimuli.

Diagnosis

H&P
• Delirium, lethargy, and seizures may be present if the hyponatremia is severe or of rapid onset.
• Manifestations of the underlying disease may be evident (e.g., fever from an infectious process or headaches and visual field defects from an intracranial mass).
• Diminished reflexes and extensor plantar responses may occur w/severe hyponatremia.
• The pt is generally normovolemic or slightly hypervolemic; edema is absent.

Labs
• Demonstration through laboratory evaluation of excessive secretion of ADH in absence of appropriate osmotic or physiologic stimuli. Labs reveal:
  • Hyponatremia
  • Urinary osmolarity > serum osmolarity
  • Urinary sodium >30 mEq/L
  • NI BUN, Cr (indicative of nl renal function and absence of dehydration)
  • ↓ Uric acid
• For diagnostic purposes, pt should have nl thyroid, adrenal, and cardiac function and no recent or concurrent use of diuretics.
Imaging
- CXR: r/o neoplasm, pneumonia

Etiology
- Neoplasm: lung, oropharynx, stomach, duodenum, pancreas, brain, thymus, bladder, prostate, endometrium, mesothelioma, lymphoma, Ewing’s sarcoma
- Pulmonary disorders: pneumonia, aspergillosis, pulmonary abscess, TB, bronchiectasis, emphysema, CF, status asthmaticus, respiratory failure associated w/positive-pressure breathing
- Intracranial disease: trauma, neoplasms, infections (meningitis, encephalitis, brain abscess), hemorrhage, hydrocephalus, MS, CGB
- Postoperative period: surgical stress, ventilators w/positive pressure, anesthetic agents
- Drugs: nicotine, chlorpropamide, thiazide diuretics, vasopressin, desmopressin, oxytocin, chemotherapeutic agents (vincristine, vinblastine, cyclophosphamide), carbamazepine, phenothiazines, MAOIs, tricyclic antidepressants, narcotics, nicotine, clofibrate, haloperidol, SSRI, NSAIDs
- Other: acute intermittent porphyria, myxedema, psychosis, delirium tremens, ACTH deficiency (hypopituitarism), general anesthesia, endurance exercise

Treatment
- In emergency situations (seizures, coma), SIAD can be treated w/combination of
  - Hypertonic saline solution (slow infusion of 250 mL of 3% NaCl). Infuse 3% saline (513 mmol/L) at a rate of 1-2 mL/kg of BW per hour to ↑ serum sodium by 1-2 mmol/L/hr.
  - Furosemide, 20-40 mg IV: ↑ the serum sodium concentration by causing diuresis of urine that is more dilute than plasma and prevents extracellular fluid volume expansion.
- The rapidity of correction varies according to the degree of hyponatremia and if the hyponatremia is acute or chronic; in general, the serum sodium concentration should be corrected only halfway to nl in the initial 24 hr. A prudent approach is to ↑ serum sodium concentration by <0.5 mEq/L/hr and to limit the total ↑ to 8-12 mmol/L during the first 24 hr.
- Close monitoring of the rate of correction (every 2-3 hr) is recommended to avoid overcorrection. In pts w/hyponatremia of chronic duration, correction of serum sodium level by >12 mmol/L during a period of 24 hr ↑ risk of osmotic demyelination.
- Conivaptan (20-40 mg/day IV) or tolvaptan (15 mg PO initially) are selective arginine vasopressin (AVP) antagonists: useful in selected hospitalized pts w/moderate to severe hyponatremia. Potential problems associated w/ their use are infusion-site reactions (50% of pts) and risk of osmotic demyelination if serum sodium levels are corrected too rapidly.
- Chronic Rx:
  - Depending on the underlying cause, fluid restriction may be needed indefinitely. Monthly monitoring of electrolytes is recommended in pts w/chronic SIAD.
  - Demeclocycline 300-600 mg PO bid: useful in pts w/chronic SIAD (e.g., secondary to neoplasm), but use w/caution in pts w/hepatic disease; side effects include nephrogenic DI and photosensitivity. This medication is also very expensive.
  - Successful treatment of chronic nephrogenic SIAD w/urea to induce osmotic diuresis has been reported in children and adults. However, oral intake of urea (30 g/day) is generally poorly tolerated.

Clinical Pearl
- SIAD is the most frequent cause of hyponatremia (50% of hyponatremia in hospital setting).
**SYPHILIS**

**Definition**
Systemic infectious disease caused by *T. pallidum*. Latent syphilis is defined as syphilis characterized by seroreactivity w/o other evidence of disease. Tertiary syphilis refers to gummatous and CV syphilis, but not to neurosyphilis.

**Diagnosis**

**H&P**
- Primary infection: ulcer or chancre at site of infection
- Secondary infection: rash, mucocutaneous lesions, and adenopathy
- Tertiary infection: cardiac, neurologic, ophthalmic, auditory, or gummatous lesions

**Labs**
- Darkfield examinations and DFA tests of lesion exudate or tissue
- Presumptive dx is possible w/the use of 2 types of serologic tests for syphilis: (1) nontreponemal (e.g., VDRL and rapid plasma reagin) and (2) treponemal (e.g., FTA-ABS and microhemagglutination assay for Ab to *T. pallidum*). The use of one type of test alone is not sufficient for dx.

**Treatment**
- Early (primary, secondary, early latent): PCN G benzathine 2.4 million U IM × 1 or doxycycline 100 mg PO bid × 14 days (alternative Rx, f/up mandatory)
- Late (late latent, CV, gumma): PCN G benzathine 2.4 million U IM q wk × 3 wk or doxycycline 100 mg PO bid × 4 wk
- Neurosyphilis: aqueous crystalline PCN G 18-24 million U/day, administered as 3-4 million U IV q4h × 10-14 days, or procaine PCN 2.4 million U IM/day, plus probenecid 500 mg PO qid, both for 10-14 days
- Congenital syphilis: aqueous crystalline PCN G 50,000 U/kg/dose IV q12h × first 7 days of life and q8h after that for total of 10 days, or procaine PCN G 50,000 U/kg/dose IM/day × 10 days
- PCN-allergic pts w/primary or secondary syphilis: doxycycline 100 mg PO bid × 14 days, or tetracycline 500 mg PO qid × 14 days, or ceftriaxone 1 g IM or IV × 8-10 days
- Latent syphilis in PCN-allergic pt: doxycycline 100 mg PO bid or tetracycline 500 mg qid for 28 days
- Tetracyclines are contraindicated in pregnancy. If the pt is pregnant and PCN allergic, she must be desensitized.

**SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)**

**Definition**
Chronic multisystemic disease characterized by production of auto-Abs and protean clinical manifestations.

**Diagnosis**
Dx made by demonstrating the presence of ≥4 of the following criteria of the American Rheumatism Association:
- Butterfly rash
- Discoïd rash
- Photosensitivity (particularly leg ulcerations)
- Oral ulcers
- Arthritis
- Serositis (pleuritis, pericarditis)
- Renal disorder (persistent proteinuria >0.5 g/day or 3+ if quantitation not performed, cellular casts)
- Neurologic disorder (seizures, psychosis [in absence of offending drugs or metabolic derangement])
- Hematologic disorder:
  - Hemolytic anemia w/reticulocytosis
  - Leukopenia (<4000/mm³ total on two or more occasions)
  - Lymphopenia (<1500/mm³ on two or more occasions)
  - Thrombocytopenia (<100,000/mm³ in the absence of offending drugs)
Diseases

Chapter 3  Diseases and Disorders

- Immunologic disorder:
  - Positive SLE cell preparation
  - Anti-DNA (presence of Ab to native DNA in abnl titer)
  - Anti-Sm (presence of Ab to Smith nuclear antigen)
  - False-positive serologic test results for syphilis known to be positive for at least 6 mo and confirmed by negative *Treponema pallidum* immobilization or FTA test results

- ANA: an abnl titer of ANA by immunofluorescence or equivalent assay at any time in the absence of drugs known to be associated w/“drug-induced lupus” syndrome

**H&P**

- Skin: erythematous rash over the malar eminences, generally w/sparring of the nasolabial folds (butterfly rash); alopecia; raised erythematosus patches w/subsequent edematous plaques and adherent scales (discoid lupus); leg, nasal, or oropharyngeal ulcerations; livedo reticularis; pallor (from anemia); petechiae (from thrombocytopenia)
- Joints: tenderness, swelling, or effusion, generally involving peripheral joints
- Cardiac: pericardial rub (in pts w/ pericarditis), heart murmurs (if endocarditis or valvular thickening or dysfunction)
- Other: fever, conjunctivitis, dry eyes, dry mouth (sicca syndrome), oral ulcers, abd tenderness, ↑ breath sounds (pleural effusions)

**Labs**

Initial labs:
- ANA, anti-DNA Ab, anti-Sm Ab
- CBC w/diff, platelet count, U/A (24-hr urine collection for protein if proteinuria is detected), PTT and ACLs in pts w/thrombotic events, BUN, Cr

**Imaging**

- CXR
- Echo: r/o valvular heart disease (present in 18% of pts w/SLE)

**Treatment**

- Joint pain and mild serositis: NSAIDs; antimalarials (e.g., hydroxychloroquine)
- Skin manifestations:
  - Topical corticosteroids; intradermal corticosteroids are helpful for individual discoid lesions, especially in the scalp.
  - Antimalarials
  - Sunscreens that block UVA and UVB radiation
  - Immunosuppressive drugs (MTX or azathioprine)
- Renal disease: glucocorticoids
  - High pulsed doses of cyclophosphamide given at monthly intervals
  - Combination of methylprednisolone and cyclophosphamide
  - For pts w/proliferative lupus nephritis: short-term Rx w/IV cyclophosphamide followed by maintenance Rx w/mycophenolate mofetil or azathioprine
  - Rapidly progressive renal failure or life-threatening systemic vasculitis: plasmapheresis in combination w/immunosuppressive agents (to prevent the rebound phenomenon of Ab levels after plasmapheresis)
- CNS involvement: corticosteroids. Anticonvulsants and antipsychotics are also indicated in selected cases; headaches are treated symptomatically.
- Hemolytic anemia: high doses of corticosteroids; nonhemolytic anemia (secondary to chronic disease) does not require specific Rx.
- Thrombocytopenia: corticosteroids
  - Danazol, vincristine, and immunoglobulins: in pts w/poor response to steroids
  - Combination chemotherapy w/cyclophosphamide and prednisone combined w/vincristine, vincristine and procarbazine, or etoposide: in pts w/severe refractory idiopathic thrombocytopenic purpura
  - Splenectomy generally does not cure the thrombocytopenia of SLE, but it may be necessary as an adjunct in managing selected cases.
Clinical Pearl
- Newer treatment modalities include the use of rituximab in pts unresponsive to conventional agents.

TAKAYASU’S ARTERITIS

Definition
Chronic systemic granulomatous vasculitis of unknown etiology primarily affecting large arteries (aorta and its branches).

Diagnosis
Criteria by the American College of Rheumatology
Takayasu’s arteritis is diagnosed if ≥3 criteria are present (sensitivity 90%, specificity 98%):
- Age at disease onset <40 yr
- Claudication of extremities
- Brachial artery pulse
- Systolic BP difference >10 mm Hg between left and right arms
- Bruit over subclavian arteries or aorta
- Abnl arteriogram

H&P
Takayasu’s arteritis most frequently involves the aortic arch and its branches and can be manifested as
- Arm claudication, weakness, and numbness
- Amaurosis fugax, diplopia, headache, and postural dizziness
- Systemic sx: low-grade fever, malaise, weight loss, fatigue, arthralgia, and myalgias
- Vascular bruits of the carotid artery, subclavian artery, and aorta
- Discrepancy of BP between the UEs
- Absent pulses
- HTN
- Retinopathy
- AI murmur

Labs
- CBC: ↑ WBC count
- ↑ ESR

Imaging
- Carotid, thoracic, and abd U/S
- Doppler and noninvasive UE and LE studies
- CT of aorta
- Aortic angiography

Treatment
- Prednisone 40-60 mg PO qd or 1 mg/kg/day is used for 3 mo.
- MTX
- Cyclophosphamide

THORACIC OUTLET SYNDROME

Definition
UE sx due to neurovascular compression at the thoracic outlet; 3 types are described on the basis of the point of compression: (1) cervical rib and scalenus syndrome, in which abnl scalene muscles or the presence of a cervical rib may cause compression; (2) costoclavicular syndrome, in which compression may occur under the clavicle; and (3) hyperabduction syndrome, in which compression may occur in the subcoracoid area.

Diagnosis
H&P
Sx and signs are related to the degree of involvement of each of the various structures at the level of the first rib.
- Arterial compression: pallor, paresthesias, diminished pulses, coolness, digital gangrene, and a supraclavicular bruit or mass
- Venous compression: edema and pain; thrombosis causing superficial venous dilation about the shoulder
“True” neural compression: lower trunk (C8, T1) findings w/intrinsic weakness and diminished sensation to the 4th and 5th hand digits and ulnar aspect of the forearm
- Possible supraclavicular tenderness
- Provocative tests (Adson’s, Wright’s): may reproduce pain but are of disputed usefulness

Imaging
- Arteriography or venography
- C-spine x-ray
- CXR
- EMG, NCV

Etiology
- Congenital cervical rib or fibrous extension of cervical rib
- Abnl scalene muscle insertion
- Drooping of shoulder girdle resulting from generalized hypotonia or trauma
- Narrowed costoclavicular interval as a result of downward and backward pressure on shoulder (sometimes seen in individuals who carry heavy backpacks)
- Acute venous thrombosis w/exercise (effort thrombosis)
- Bone abnormalities of first rib
- Abnl fibromuscular bands
- Malunion of clavicle Fx

Treatment
- Sling for pain relief
- Physical therapy modalities plus shoulder girdle–strengthening exercises
- Postural re-education
- NSAIDs
- Surgery: for vascular disorders

365 THROMBOCYTHEMIA, ESSENTIAL (ET)

Definition
Chronic myeloproliferative disorder characterized by a sustained proliferation of megakaryocytes, which leads to ↑ numbers of circulating platelets, profound marrow megakaryocyte hyperplasia, splenomegaly, and a course punctuated by hemorrhagic or thrombotic episodes or both.

Diagnosis
H&P
- Many pts are asymptomatic and reach medical attention fortuitously as a result of extreme thrombocytosis detected on routine CBC.
- Neurologic: headaches, TIAs, paresthesias of extremities
- Small- or large-vessel thrombosis or minor bleeding, gangrene of toes, digital pain, erythromelalgia (syndrome of redness and burning pain of extremities)

Labs
- Thrombocytosis due to ↑ platelet production by megakaryocytes
- Leukocytosis, eosinophilia, basophilia
- ↑ Uric acid (25%)
- The JAK2 V617F mutation (40%-60%)
- ↑ Bleeding time (7%-19%)
- Bone marrow bx: proliferation mainly of the megakaryocytic lineage w/↑ numbers of enlarged, mature megakaryocytes; no significant ↑ or left shift of neutrophil granulopoiesis or erythropoiesis

Treatment
- Reduction of platelet count to <500,000/mm³
- Rapid platelet pheresis in combination w/the institution of myelosuppressive Rx in pts w/life-threatening hemorrhagic or thrombotic episodes
- Hydroxyurea, interferon alfa, anagrelide, and pegylated interferon are commonly used agents.
- Low-dose ASA in pts w/thrombosis or erythromelalgia
THROMBOCYTOPENIA

Definition
Platelet count <150,000/mm³.

Diagnosis
**Diagnostic Approach** (Fig. 3-46)
- Thorough hx (particularly drug hx)
- PE: evaluate for presence of splenomegaly (hypersplenism, leukemia, lymphoma)

**Labs**
- Examine peripheral blood smear; note platelet size and other abnormalities (e.g., fragmented RBCs may indicate TTP or DIC; ↑ platelet size suggests accelerated destruction and release of large young platelets into the circulation).
- Check INR, PTT, bleeding time, Coombs’ test.
- Bone marrow examination: ↑ megakaryocytes indicate thrombocytopenia resulting from accelerated destruction.

**Etiology**

**↑ Destruction:**
- Immunologic
  - Drugs: quinine, quinidine, digitalis, procainamide, thiazide diuretics, sulfonamides, phenytoin, ASA, PCN, heparin, gold, meprobamate, sulfa drugs, phenylbutazone, NSAIDs, methyldopa, cimetidine, furosemide, INH, cephs, chlorpropamide, organic arsenicals, chloroquine, platelet glycoprotein IIb/IIIa receptor inhibitors, ranitidine, indomethacin, carboplatin, ticloididine, clopidogrel
- ITP
- Transfusion reaction: transfusion of platelets w/plasminogen activator (PLA) in recipients w/o PLA-1
- Fetal/maternal incompatibility
- Collagen-vascular diseases (e.g., SLE)
- AIHA
- Lymphoreticular disorders (e.g., CLL)
- Nonimmunologic
  - Prosthetic heart valves
  - TTP

**R/o**

- Drug-induced
- Clumped platelets
- Isolated thrombocytopenia
- Ancillary labs
- Stop offending agent and repeat platelet count
- Positive antiplatelet Ab
- R/o ITP
- ↑ LDH, schistocytes on peripheral smear
- R/o TTP
- ↑ PTT, D-dimer, fibrinogen
- R/o DIC
- Normal
- Bone marrow exam
- R/o Evans syndrome
- Bone marrow exam
- Coombs’ positive hemolytic anemia
- R/o Evans syndrome
- Nonhemolytic anemia

**Figure 3-46.** Diagnostic algorithm for thrombocytopenia.
• Sepsis
• DIC
• HUS
• Giant cavernous hemangioma

**Production:**
- Abnl marrow
- Marrow infiltration (e.g., leukemia, lymphoma, fibrosis)
- Marrow suppression (e.g., chemotherapy, alcohol, irradiation)
- Vitamin deficiencies (B₁₂, folate)
- Hereditary disorders
  - Wiskott-Aldrich syndrome: X-linked disorder characterized by thrombocytopenia, eczema, and repeated infections
  - May-Hegglin anomaly: ↑ megakaryocytes but ineffective thrombopoiesis

**Splenic sequestration**

**Hypersplenism**

**Dilutional (massive transfusion)**

### 367 THROMBOPHLEBITIS, SUPERFICIAL

**Definition**
Inflammatory thrombosis in SC veins. *Superficial suppurative thrombophlebitis* is an inflammation of the vein wall due to the presence of microorganisms occurring as a complication of either dermal infection or use of an indwelling IV catheter.

**Diagnosis**

**H&P**
- SC vein is palpable, tender; tender cord is present w/erythema and edema of the overlying skin and SC tissue.
- Induration, redness, and tenderness are localized along the course of the vein. This linear appearance rather than circular appearance is useful to distinguish thrombophlebitis from other conditions (cellulitis, erythema nodosum).
- There is no significant swelling of the limb (superficial thrombophlebitis generally does not produce swelling of the limb).
- Low-grade fever may be present. High fever and chills are suggestive of septic phlebitis.

**Labs**
- CBC w/diff
- Blood cultures
- Culture of IV catheter tip (when secondary to IV cannulation)

**Imaging**
- Serial U/S or venography in pts w/suspected DVT
- CT scan of abd in pts w/suspected malignant neoplasm (Trousseau’s syndrome: recurrent migratory thrombophlebitis)

**Etiology**
- Trauma to preexisting varices
- IVs (most common cause)
- Abd cancer (e.g., carcinoma of pancreas)
- Infection (*Staphylococcus* is the most common pathogen)
- Hypercoagulable state
- DVT

**Treatment**
- Warm, moist compresses
- It is not necessary to restrict activity; however, if there is extensive thrombophlebitis, bed rest w/the leg elevated will limit the thrombosis and improve sx.
- NSAIDs to relieve sx
- Treatment of septic thrombophlebitis w/abx w/adequate coverage of Enterobacteriaceae and *Staphylococcus*; initial empiric treatment w/a semisynthetic PCN (IV nafcillin 2 g q4-6h + either an AG [gentamicin 1 mg/kg IV q8h] or a third-generation ceph [cefotaxime] or a quinolone [ciprofloxacin])
Ligation and division of the superficial vein at the junction to avoid propagation of the clot in the deep venous system when the thrombophlebitis progresses toward the junction of the involved superficial vein w/deep veins.

The role of antifungal Rx for superficial suppurative thrombophlebitis due to *C. albicans* is controversial. Most of these infections can be cured by vein excision. Because of the propensity of these infections for hematogenous spread, a 10- to 14-day course of amphotericin B or fluconazole is advisable.

**Clinical Pearls**

- 20% of superficial thrombophlebitis cases are associated w/occult DVT.
- Catheter-related thrombophlebitis incidence is 100:100,000. The disease occurs more frequently when plastic catheters are inserted in the lower extremities. The mean duration of preceding venous cannulation is 4.8 days, and the latent interval from removal of the catheter to development of sx ranges from 2-10 days.

### 368 THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

**Definition**

Rare disorder characterized by thrombocytopenia (often accompanied by purpura) and microangiopathic hemolytic anemia; neurologic impairment, renal dysfunction, and fever may also be present.

**Diagnosis**

**H&P**

- Most pts present w/nonspecific constitutional sx (weakness, nausea, abd pain, vomiting)
- Purpura (secondary to thrombocytopenia)
- Jaundice, pallor (secondary to hemolysis)
- Mucosal bleeding
- Fever
- Fluctuating levels of consciousness (secondary to thrombotic occlusion of the cerebral vessels)
- Renal failure and neurologic events are usually end-stage features.

**Labs**

- Severe anemia and thrombocytopenia (platelet count <50,000 or >50% ↓ from previous count)
- ↑ BUN and Cr
- Evidence of hemolysis: ↑ reticulocyte count, indirect bili, LDH, ↓ haptoglobin
- U/A: hematuria (red cells and red cell casts in urine sediment), proteinuria
- Peripheral smear: severely fragmented RBCs (schistocytes); >4% red blood cell fragments in the peripheral blood
- No laboratory evidence of DIC (nl FDP, fibrinogen)
- The ADAMTS13 level is not necessary, and metalloproteinase deficiency need not be proved for dx of TTP.

**Etiology**

- TTP is caused in some pts by an acquired deficiency of a circulating metalloproteinase. It can also be caused in very rare cases by a hereditary deficiency of ADAMTS13.
- Many drugs, including clopidogrel, PCN, antineoplastic agents, oral contraceptives, quinine, and ticlopidine, have been associated w/TTP. Other precipitating causes include infectious agents, pregnancy, malignant neoplasms, allogeneic bone marrow transplantation, and neurologic disorders.

**Treatment**

- Discontinue potential offending agents.
- The American Association of Blood Banks, the American Society for Apheresis, and the British Committee for Standards in Haematology recommend daily plasma exchange w/replacement of 1.0-1.5× the predicted plasma volume of the pt as standard Rx for TTP. The British
guidelines recommend that plasma exchange Rx be continued for a minimum of 2 days after the platelet count returns to nl (>150,000/cm³).

- Use of corticosteroids (prednisone 1-2 mg/kg/day) is controversial. They may be effective alone in pts w/mild disease or may be administered concomitantly w/plasmapheresis + plasma exchange w/FFP.
- High-dose plasma infusion (25 mL/kg/day) may be useful only if plasma exchange cannot be promptly started and for pts w/very severe or refractory disease between plasma exchange sessions. High-dose plasma infusions can cause volume overload in pts w/renal insufficiency.
- The monoclonal Ab rituximab has also been used for treatment of TTP.
- Platelet transfusions are contraindicated except in severely thrombocytopenic pts w/documentated bleeding.
- Use of antiplatelet agents (ASA, dipyridamole) is controversial.
- Splenectomy is performed in refractory cases.

### 369 THYROID NODULE

**Definition**
Abnl growth of the thyroid gland; nodules can be benign (70%) or malignant.

**Diagnosis**

**H&H**
- Palpable, firm, and non-tender nodule in the thyroid area should prompt suspicion of carcinoma. Signs of metastasis are regional lymphadenopathy, inspiratory stridor.
- Signs and sx of thyrotoxicosis can be found in functioning nodules.

**Labs**
- FNAB: best dx study; the accuracy can be >90%, but it is directly related to the level of experience of the physician and the cytopathologist interpreting the aspirate.
- FNAB is less reliable w/thyroid cystic lesions; surgical excision should be considered for most thyroid cysts not abolished by aspiration.
- TSH, T₄, and serum thyroglobulin levels: should be obtained before thyroidectomy in pts w/confirmed thyroid carcinoma on FNAB.
- Serum calcitonin level at random or after pentagastrin stimulation: useful when medullary carcinoma of the thyroid is suspected and in anyone w/FHX of medullary thyroid carcinoma.
- Serum thyroid auto-Abs: useful when thyroiditis is suspected.

**Imaging**
- Thyroid U/S to evaluate the size of the thyroid and the number, composition (solid vs. cystic), and dimensions of the thyroid nodule; solid thyroid nodules have a higher incidence of malignancy, but cystic nodules can also be malignant.
- Thyroid scan w/technetium Tc 99m pertechnetate:
  - Classifies nodules as hyperfunctioning (hot), normally functioning (warm), or nonfunctioning (cold); cold nodules have a higher incidence of malignancy.
  - Scan has difficulty evaluating nodules near the thyroid isthmus or at the periphery of the gland.
  - NI tissue over a nonfunctioning nodule might mask the nodule as “warm” or normally functioning.

**Treatment**
- Depends on results of FNAB
- NI cells: may repeat bx during present evaluation or re-evaluate pt after 3-6 mo of suppressive Rx (L-thyroxine, prescribed in doses to suppress the TSH level to 0.1-0.5). Failure to regress indicates ↑ likelihood of malignancy. Reliance on repeated needle bx is preferable to routine surgery for nodules not responding to thyroxine.
- Malignant cells: surgery
- Hypercellularity: thyroid scan
  - Hot nodule: ¹³¹I Rx if the pt is hyperthyroid
  - Warm or cold nodule: surgery (r/o follicular adenoma vs. carcinoma)
Clinical Pearl

- ↑ Likelihood that nodule is malignant: nodule ↑ in size or >2 cm, regional lymphadenopathy, fixation to adjacent tissues, age <40 yr, sx of local invasion (dysphagia, hoarseness, neck pain, male sex, FHx of thyroid cancer or polyposis (Gardner’s syndrome).

370 THYROIDITIS

Definition

Inflammatory disease of the thyroid. Thyroiditis can be subdivided into 3 common types (Hashimoto’s, painful, painless) and 2 rare forms (suppurative, Riedel’s). To add to the confusion, there are various synonyms for each form, and there is no internationally accepted classification of autoimmune thyroid disease.

Diagnosis

H&P

- Hashimoto’s: pts may have signs of hyperthyroidism (tachycardia, diaphoresis, palpitations, weight loss) or hypothyroidism (fatigue, weight gain, delayed reflexes), depending on the stage of the disease. Usually there is diffuse, firm enlargement of the thyroid gland; thyroid gland may also be of nl size (atrophic form wclinically manifested hypothyroidism).

- Painful subacute: exquisitely tender, enlarged thyroid, fever; signs of hyperthyroidism are initially present; signs of hypothyroidism can subsequently develop.

- Painless: clinical features are similar to those of subacute thyroiditis except for the absence of tenderness of the thyroid gland.

- Suppurative: pt is febrile w/severe neck pain, focal tenderness of the involved portion of the thyroid, erythema of the overlying skin.

- Riedel’s: slowly enlarging hard mass in the anterior neck; often mistaken for thyroid cancer; signs of hypothyroidism occur in advanced stages.

Labs

- TSH, free T4: may be nl or indicative of hypothyroidism or hyperthyroidism, depending on the stage of the thyroiditis

- WBC w/diff: ↑ WBC w/shift to the left w/subacute and suppurative thyroiditis

- Antimicrosomal Abs: detected in >90% of pts w/Hashimoto’s thyroiditis and 50%-80% of pts w/silent thyroiditis

- Serum thyroglobulin levels: ↑ in pts w/subacute and silent thyroiditis; this test is nonspecific but may be useful in monitoring the course of subacute thyroiditis and distinguishing silent thyroiditis from factitious hyperthyroidism (low or absent serum thyroglobulin level).

Imaging

- 24-hr RAIU uptake (RAIU): useful to distinguish Graves’ disease (↑ RAIU) from thyroiditis (nl or ↓ RAIU)

Etiology

- Hashimoto’s: autoimmune disorder that begins w/the activation of CD4 (helper) T-lymphocytes specific for thyroid antigens. The etiologic factor for the activation of these cells is unknown.

- Painful subacute: possibly postviral; usually follows a respiratory illness; it is not considered to be a form of autoimmune thyroiditis.

- Painless: frequently occurs post partum

- Suppurative: infectious etiology, generally bacterial, although fungi and parasites have also been implicated; it often occurs in immunocompromised hosts or after a penetrating neck injury.

- Riedel’s: fibrous infiltration of the thyroid; etiology is unknown.

- Drug induced: lithium, interferon alfa, amiodarone, interleukin-2

Treatment

- Treat hypothyroid phase w/levothyroxine 25-50 µg/day initially and monitor serum TSH initially every 6-8 wk.

- Control sx of hyperthyroidism w/β-blockers (e.g., propranolol 20-40 mg PO q6h).
Control pain in pts w/subacute thyroiditis w/NSAIDs. Prednisone 20-40 mg qd may be used if NSAIDs are insufficient, but it should be gradually tapered off during several weeks.

Use IV abx and drain abscess (if present) in pts w/ suppurative thyroiditis.

**Clinical Pearls**
- In Hashimoto’s thyroiditis, long-term prognosis is favorable; most pts recover their thyroid function.
- In painful subacute thyroiditis, permanent hypothyroidism occurs in 10% of pts.
- In painless thyroiditis, 6% of pts have permanent hypothyroidism.

### THYROTOXIC STORM

**Definition**
Abrupt and severe exacerbation of thyrotoxicosis.

**Diagnosis**

**H&P**
- Tremor, tachycardia, fever
- Warm, moist skin
- Lid lag, lid retraction, proptosis
- ΔMS (psychosis, coma, seizures)

**Labs**
- ↑ Free T₄, ↓ TSH
- CBC w/diff
- Blood and urine cultures
- Glucose
- Liver enzymes
- BUN, Cr
- Serum Ca
- CPK

**Differential Diagnosis**
- Psychiatric disorders
- Alcohol or other drug withdrawal
- Pheochromocytoma
- Metastatic neoplasm

**Treatment**
- Inhibition of thyroid hormone synthesis: methimazole 80-100 mg PO or PR followed by 30 mg PR q8h.
- Inhibition of stored thyroid hormone
  - Iodide can be administered as sodium iodine, 250 mg IV q6h; potassium iodide (SSKI), 5 gtt PO q8h; or Lugol’s solution, 10 gtt q8h. Administer methimazole 1 hr before the iodide to prevent the oxidation of iodide to iodine and its incorporation in the synthesis of additional thyroid hormone.
  - Corticosteroids: dexamethasone 2 mg IV q6h or hydrocortisone 100 mg IV q6h × 48 h to inhibit thyroid hormone release, to impair peripheral conversion of T₂ from T₄, and to provide additional adrenocortical hormone to correct deficiency (if present).
- Suppression of peripheral effects of thyroid hormone: β-adrenergic blockers: propranolol 80 to 120 mg PO q4-6h. Propranolol may also be given IV 1 mg/min for 2-10 min under continuous ECG and BP monitoring.
- Control of fever w/acetaminophen 325-650 mg q4h; avoid ASA because it displaces thyroid hormone from its binding protein.
- Treatment of any precipitating factors (e.g., abx if infection is strongly suspected)

### TINEA CRURIS

**Definition**
Dermatophyte infection of the groin caused by dermatophytes of the genera *Trichophyton*, *Epidermophyton*, and *Microsporum*. *T. rubrum* and *E. floccosum* are the most common causes.
**Diagnosis**

**H&P**
- Erythematous plaques have a half-moon shape and a scaling border.
- The acute inflammation tends to move down the inner thigh and usually spares the scrotum; in severe cases, the fungus may spread onto the buttocks.
- Itching may be severe.
- Red papules and pustules may be present.
- An important diagnostic sign is the advancing well-defined border w/a tendency toward central clearing.

**Labs**
- Hyphae detected with potassium hydroxide

**Treatment**
- Topical antifungal agents (butenafine or terbinafine cream) for mild cases
- PO antifungals: fluconazole 200 mg qd and terbinafine 250 mg qd × 7-10 days
- Drying powders (e.g., miconazole nitrate) may be useful in pts w/excessive perspiration.

**Clinical Pearl**
- Pt’s feet should be evaluated as a source of infection because tinea cruris is often associated w/tinea pedis.

**TORSADES DE POINTES**

**Definition**
Form of VT manifested by episodes of alternating electrical polarity, w/the amplitude of the QRS complex twisting around an isoelectric baseline resembling a spindle (Fig. 3-47); rhythm usually starts w/a PVC and is preceded by widening of the QT interval.

![FIGURE 3-47. Torsades de pointes.](image)

**Etiology**
- Torsades may be caused by electrolyte disturbances (hypokalemia, hypomagnesemia, hypocalcemia), antiarrhythmic drugs that prolong the QT interval (procainamide, quinidine, disopyramide), N-acetylprocainamide, droperidol, amiodarone, phenothiazines, haloperidol, tricyclic antidepressants, terfenadine, astemizole, ketoconazole, erythromycin, TMP-SMZ, high-dose methadone, or cocaine. Torsades de pointes is also associated w/hereditary long QT interval syndromes.

**Treatment**
- Electrical termination of the tachycardia w/cardioversion when the ventricular tachyarrhythmia is sustained
- IV infusion of isoproterenol to ↓ the QT interval and to prevent recurrences
- Elimination of contributing factors (correction of electrolyte abnormalities, discontinuation of suspected drugs); early dx of hereditary LQTS and treatment w/β1-adrenergic receptor blocking agents. Surgical sympathectomy and use of ICDs should also be considered in high-risk pts w/hereditary LQTS.
Diseases

TOXIC SHOCK SYNDROME (TSS)

Definition
Acute febrile illness resulting in multiple organ system dysfunction caused most commonly by a bacterial exotoxin.

Diagnosis
H&P
- Fever (>38.9°C)
- Diffuse macular erythematous rash that desquamates 1-2 wk after disease onset in survivors
- Orthostatic hypotension
- GI sx: vomiting, diarrhea, abd tenderness
- Constitutional sx: myalgia, headache, photophobia, rigors, altered sensorium, conjunctivitis, arthralgia
- Respiratory sx: dysphagia, pharyngeal hyperemia, strawberry tongue
- GU sx: vaginal d/c, vaginal hyperemia, adnexal tenderness
- End-organ failure
- Severe hypotension and ARF
- Hepatic failure
- CV sx: DIC, pulmonary edema, ARDS, endomyocarditis, heart block

Labs
- Pan culture (cervix/vagina, throat, nasal passages, urine, blood, CSF, wound) for *Staphylococcus, Streptococcus*, or other pathogenic organisms
- Electrolytes to detect hypokalemia, hyponatremia
- CBC w/diff, PT, PTT
- Protein, AST, ALT, hypocalcemia, BUN/Cr, hypophosphatemia, LDH, CPK
- U/A: WBC (>5/hpf), proteinemia, microhematuria
- ABGs to assess respiratory function and acid-base status
- Serologic tests considered for RMSF, Lyme disease, rubeola, and leptospirosis

Imaging
- CXR
- Sonography, CT scan, MRI: if abd/pelvic abscess suspected

Etiology
- Menstrually associated TSS: 45% of cases associated w/tampons, diaphragm, or vaginal sponge use
- Non–menstruating-associated TSS: 55% of cases associated w/puerperal sepsis, post–cesarean section endometritis, mastitis, wound or skin infection, insect bite, PID, and postoperative fever
- Causative agent: *S. aureus* infection of a susceptible individual (10% of population lacking sufficient levels of antitoxin Abs), which liberates the disease mediator TSST-1 (exotoxin)
- Other causative agents: coagulase-negative streptococci producing enterotoxins B or C, and exotoxin A producing group A beta-hemolytic streptococci

Treatment
- Aggressive fluid resuscitation (maintenance of circulating volume, CO, BP)
- Thorough search for a localized infection or nidus: I&D, débridement, removal of tampon or vaginal sponge
- Central hemodynamic monitoring: Swan–Ganz catheter and A-line for surveillance of hemodynamic status and response to Rx
- Foley catheter to monitor hourly urine output
- Possible MAST trousers as temporary measure
- Acute ventilator management if severe respiratory compromise
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- Renal dialysis for severe renal impairment
- Surgical intervention for indicated conditions (i.e., ruptured tubo-ovarian abscess, wound abscess, mastitis)
- Isotonic crystalloid (NS solution) for volume replacement following “7-3” rule
- Electrolyte replacement (K+, Ca+)
- PRBC, coagulation factor replacement, or FFP to treat anemia or D&C
- Vasopressor Rx for hypotension refractory to fluid volume replacement (i.e., dopamine beginning at 2-5 µg/kg/min)
- Naloxone infusion (i.e., 0.5 mg/kg/hr) to improve BP by blocking endogenous endorphin effects
- Parenteral abx Rx; β-lactamase–resistant abx (methicillin, nafcillin, or oxacillin) initiated early
- Broad-spectrum abx added if concurrent sepsis suspected
- Doxycycline added if RMSF is being considered

375 TRANSFUSION REACTION

Treatment
- Stop transfusion immediately.
- Maintain IV access, BP, HR, adequate airway.
- Induce diuresis w/0.9% NS or other crystalloid solution to maintain urine output ≥100 mL/hr for at least 24 hr.
- Give diuretic (furosemide). Consider alkalization of urine by adding sodium bicarbonate to ↑ urinary pH to >7.5 to improve excretion of free Hgb.
- Monitor BUN, Cr, PT, APTT, fibrinogen, LDH, bili, haptoglobin.
- Blood bank w/u: check paperwork, observe plasma for Hgburia, repeat serologic testing (ABO, Rh), repeat crossmatch, perform direct antiglobulin test, analyze urine for hemoglobinuria.

376 TRANSIENT ISCHEMIC ATTACK (TIA)

Definition
Transient neurologic dysfunction caused by focal brain or retinal ischemia w/sx typically lasting <60 min and followed by a full recovery of function. Acute brain ischemia is a medical emergency requiring prompt neurologic evaluation and potential intervention.

Diagnosis
H&P
- Neurologic abnormalities are confined to discrete vascular territory (Boxes 3-11 and 3-12)

Imaging
- Head CT
- Brain MRI, MRA

Box 3-11 • Characteristics of Carotid Artery Syndrome

Ipsilateral monocular vision loss (amaurosis fugax); the pt often feels as if “a shade” has come down over one eye
- Episodic contralateral arm, leg, and face paresis and paresthesias
- Slurred speech, transient aphasia
- Ipsilateral headache of vascular type
- Carotid bruit may be present over the carotid bifurcation
- Microemboli, hemorrhages, and exudates may be noted in the ipsilateral retina

Box 3-12 • Characteristics of Vertebral Artery Syndrome

Binocular visual disturbances (blurred vision, diplopia, total blindness)
- Vertigo, N/V, tinnitus
- Sudden loss of postural tone of all 4 extremities (drop attacks) w/no loss of consciousness
- Slurred speech, ataxia, numbness around lips or face
Tuberculosis, Pulmonary

**Definition**
Infection of the lung and, occasionally, surrounding structures, caused by the bacterium *Mycobacterium tuberculosis*.

**Diagnosis**

**Workup**
- Sputum for AFB stains
- CXR
- PPD
  - Recent conversion from negative to positive reaction within 3 mo of exposure is highly suggestive of recent infection.
  - Single positive PPD reaction is not helpful diagnostically.
  - Negative PPD reaction: never r/o acute TB.
  - Be certain that positive PPD reaction does not reflect “booster phenomenon” (prior positive PPD reaction may become negative after several years and return to positive only after second repeated PPD;
repeat second PPD within 1 wk), which thus may mimic skin test conversion.

- Positive PPD reaction is determined as follows:
  - Induration after 72 hr of intradermal injection of 0.1 mL of 5 TU PPD
  - 5-mm induration if HIV positive (or other severe immunosuppressed state affecting cellular immune function), close contact of active TB, fibrotic chest lesions
  - 10-mm induration if in high medical risk groups (immunosuppressive disease or Rx, renal failure, gastrectomy, silicosis, diabetes), foreign-born high-risk group (Southeast Asia, Latin America, Africa, India), low socioeconomic groups, IV drug addict, prisoner, health care worker
  - 15-mm induration if low risk

- QuantiFERON test (QFT-G) is a blood test that measures interferon response to specific *M. tuberculosis* antigens. It may assist in distinguishing true positive reactions of individuals w/latent tuberculosis from PPD reactions related to non-tuberculous mycobacteria, prior BCG vaccination, or difficult-to-interpret skin test results from persons w/dermatologic conditions or immediate allergic reactions to PPD.

**Labs**

- Sputum for AFB stains and culture; induced sputum if pt not coughing productively
- Sputum from bronchoscopy if high suspicion of TB w/negative expectorated induced sputum for AFB
  - + AFB smear is essential before or shortly after treatment to ensure subsequent growth for definitive dx and sensitivity testing.
  - Consider lung bx if sputum negative, especially if infiltrates are predominantly interstitial.
- AFB stain-negative sputum may grow *M. tuberculosis* subsequently
- Gastric aspirates reliable, especially in HIV-negative pts
- CBC
  - Variable values
    - WBCs: ↓, nl, or ↑ (including leukemoid reaction: >50,000)
    - Normocytic, normochromic anemia often
  - Rarely helpful diagnostically
- ESR usually ↑
- Thoracentesis
  - Exudative effusion
    - ↑ Protein
    - ↓ Glucose
    - ↑ WBCs (polymorphonuclear leukocytes early, replaced later by lymphocytes)
    - May be hemorrhagic
  - Pleural fluid usually AFB negative
  - Pleural bx often diagnostic; may need to be repeated for dx
  - Culture pleural bx tissue for AFB
- Bone marrow bx is often diagnostic in difficult-to-dx cases, especially miliary TB

**CXR**

- Primary infection reflected by calcified peripheral lung nodule w/calcified hilar lymph node
- Reactivation pulmonary TB
  - Necrosis
  - Cavitation (especially on apical lordotic views)
  - Fibrosis and hilar retraction
  - Bronchopneumonia
  - Interstitial infiltrates
  - Miliary pattern
  - Many of preceding features may also accompany progressive primary TB.
- TB pleurisy: pleural effusion, often rapidly accumulating and massive
- TB activity not established by single CXR
- Serial CXRs are excellent indicators of progression or regression
Compliance (rigid adherence to treatment regimen) chief determinant of success. Supervised directly observed Rx (DOT) recommended for all pts and mandatory for unreliable pts.

Prefered adult regimen: DOT
- Isoniazid (INH) 15 mg/kg (max 900 mg) + rifampin 600 mg + ethambutol (EMB) 30 mg/kg (max 2500 mg) + pyrazinamide (PZA) (2 g [<50 kg]; 2.5 g [51-74 kg]; 3 g [75 kg]) qd weekly for 6 mo
- Alternative, more complicated DOT regimens

Rifapentine, a rifampin derivative w/a much longer serum half-life, was shown to be as effective when administered weekly (w/weekly isoniazid) as conventional regimens for drug-sensitive pulmonary tuberculosis in non-HIV-infected pts.

Short-course daily Rx: adult
- HIV-negative pt: 6 mo total Rx (2 mo INH 300 mg + rifampin 600 mg + EMB 15 mg/kg [max 2500 mg]) + PZA (1.5 g [<50 kg]; 2 g [51-74 kg]; 2.5 g [>75 kg]) qd and until smear negative and sensitivity confirmed; then INH + rifampin qd × 4 mo
- HIV-positive pt: 9 mo total Rx (2 mo INH + rifampin + EMB + PZA qd until smear negative and sensitivity confirmed; then INH + rifampin qd × 7 mo)
  - Continue treatment at least 3 mo after conversion to negative cultures.

Drug resistance (often multiple drug resistance [MDRTB]) by
- Prior treatment
- Acquisition of TB in developing countries
- Homelessness
- AIDS
- Prisoners
- IV drug addicts
- Known contact w/MDRTB
- Never add single drug to failing regimen.
- Never treat TB w/fewer than 2-3 drugs or 2-3 new additional drugs.
- Monitor for clinical toxicity (especially hepatitis).
  - Pt and physician awareness that anorexia, nausea, RUQ pain, and unexplained malaise require immediate cessation of treatment
  - Evaluation of LFTs; min. AST/ALT elevations w/o sx generally transient and not clinically significant

Preventive treatment for PPD conversion only (infection w/o disease)
- Must be certain that CXR is normal and pt has no sx of TB
- INH 300 mg qd for 9-12 mo; at least 12 mo if HIV positive
- Most important groups:
  - HIV-positive and other severely immunocompromised pts
  - Close contact of active TB pt
  - Recent converter
  - Old TB on CXR
  - IV drug addict
  - Medical risk factor
  - High-risk foreign country
  - Homeless

Infants are generally given prophylaxis immediately if recent contact of active TB pt (even if infant’s PPD reaction is negative), then retested w/PPD in 3 mo (continuing INH if PPD reaction becomes positive and stopping INH if PPD reaction remains negative).

Chronic, stable PPD reaction (several years) given INH prophylaxis generally only if pt is <35 yr old.
- INH toxicity may outweigh benefit.
- Individualize decision.

Preventive Rx for suspected INH-resistant organisms is unclear.

All contacts (especially close household contacts and infants) should be properly tested for PPD conversions during 3 mo after exposure.

Those w/positive PPD reaction should be evaluated for active TB and properly treated or given prophylaxis.
**378 TUMOR LYSIS SYNDROME**

**Definition**

Syndrome characterized by rapid development of ↑ uric acid, ↑ K⁺, ↑ PO₄, and ↓ Ca due to leukemic cell death secondary to chemotherapy (often seen w/high-grade lymphoma, ALL, AML chemo).

**Treatment**

- IV hydration, alkalinization of urine, and administration of allopurinol
- Allopurinol reversibly inhibits xanthine oxidase, causing a reduction of serum uric acid concentration. Brisk diuresis is required to prevent renal tubular deposition of Ca phosphate and the metabolic intermediates xanthine and hypoxanthine that accumulate during Rx w/allopurinol. Pts w/↑↑ serum uric acid level may be treated w/recombinant urate oxidase (rasburicase), which converts uric acid to soluble allantoin.

**Clinical Pearl**

- Avoid NSAIDs and IV contrast agents.

**379 ULCERATIVE COLITIS (UC)**

**Definition**

Chronic IBD of undetermined etiology.

**Diagnosis**

**H&P**

- Abd distention and tenderness
- Bloody diarrhea
- Fever, evidence of dehydration
- Evidence of extraintestinal manifestations in 25% of pts: liver disease, sclerosing cholangitis, iritis, uveitis, episcleritis, arthritis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis

**Labs**

- Anemia, ↑ ESR
- ↓ Potassium, Mg, Ca, alb
- Consider stool examinations for O&P, stool culture, and testing for *Clostridium difficile* toxin if persistent diarrhea
- (-) ASCA (anti saccharomyces cerevisiae antibody), (+) pANCA (>45% of pts). Presence or pANCA is associated w/relative resistance to medical Rx.

**Imaging**

- Imaging generally not indicated. A double-contrast barium enema study and small bowel follow-through, when used (in cases in which colonic strictures prevent a thorough evaluation), may reveal continuous involvement (including the rectum), pseudopolyps, ↓ mucosal pattern, and fine superficial ulcerations.

**Treatment**

The therapeutic options vary w/the degree of disease (mild, severe, fulminating) and areas of involvement (distal, extensive).

- Mild or moderate disease: mesalamine administered as an enema (40 mg once qd at hs for 3–6 wk) or suppository (500 mg bid) for pts w/distal colonic disease. Oral forms in which the 5-ASA is in a slow-release or pH-dependent matrix (Pentasa 1 g qid, Asacol 800 mg PO tid) can deliver therapeutic concentrations to the more proximal small bowel or distal ileum.
- Olsalazine: useful for maintenance of remission of UC in pts intolerant of sulfasalazine. Usual dose is 500 mg bid taken w/food.
- Balsalazide: indicated for mild to moderately active UC. Usual dose is three 750-mg capsules tid.
- Severe disease: corticosteroids (e.g., prednisone 40–60 mg/day); corticosteroid suppositories or enemas are also useful for distal colitis.
- Infliximab: in pts who failed corticosteroid Rx
- Fulminant disease: hospital admission and parenteral corticosteroids (e.g., IV hydrocortisone 100 mg q6h); IV cyclosporine can also be used in severe refractory cases; renal toxicity is a potential complication.
■ Surgery: indicated in pts who fail to respond to intensive medical Rx. Colectomy is usually curative in these pts and also eliminates the high risk for development of adenocarcinoma of the colon (10%-20% of pts develop it after 10 yr w/the disease).
■ Correct nutritional deficiencies; TPN w/bowel rest may be necessary in severe cases; folate supplementation may ↓ the incidence of dysplasia and cancer in chronic UC.
■ Avoid oral feedings during acute exacerbation to ↓ colonic activity; a low-roughage diet may be helpful in early relapse.
■ Psychotherapy is useful in most pts. Referral to self-help groups is also important because of the chronicity of the disease and the young age of the pts.

**Clinical Pearls**
■ Colonoscopic surveillance and multiple biopsies should be instituted approximately 10 yr after dx because of ↑ risk of colon carcinoma.
■ Erythropoietin: useful in pts w/anemia refractory to treatment w/iron and vitamins.
■ The clinical course is variable; approximately 66% of pts will achieve clinical remission w/medical Rx, and nearly 80% of treatment compliant pts maintain remission; 15%-20% of pts will eventually require colectomy; >75% of pts treated medically will experience relapse.

### URINARY TRACT INFECTION (UTI)

**Definition**

**Pyuria**, presence of >10 leukocytes/mL of uncentrifuged urine. **Bacteriuria**, presence of >100,000 bacteria/mL of urine (in urine cultures). Counts of 10,000 to 100,000/mL can also indicate infection, especially in the presence of pyuria; the growth of ≥10^5 colony-forming units per milliliter of a single predominant species reliably indicates true bacteriuria in male pts, whereas counts ≤10^5 or growth in any amount of ≥3 species, w/none predominant, nearly always represents specimen contamination. The presence of bacteria on U/A implies bacterial counts >50,000/mL.

**Diagnosis**

**Labs**
■ U/A (clean-catch specimen)
■ Urine C&S
■ Blood cultures: indicated only in suspected pyelonephritis or sepsis

**Imaging**
■ Spiral CT, cystoscopy, U/S: indicated in men w/UTI and women w/recurrent UTIs; done to r/o obstruction, calculi, and papillary necrosis

**Etiology**
■ *E. coli*: causes >90% of uncomplicated UTIs and is often found in complicated cases of UTI
■ *Proteus*: gram-negative rod that causes alkaline urine and promotes formation of struvite calculi
■ *Klebsiella*: frequent cause of uncomplicated community-acquired UTI
■ *Enterococcus*: most common gram-positive cause of UTI; often associated w/prior abx Rx, urologic instrumentation, or obstructive uropathy
■ *Pseudomonas*: often associated w/obstructive uropathy
■ *Staphylococcus* (in diabetic pts): may indicate intrarenal abscess or a “spillover” from bacteremia rather than a true UTI. *Staphylococcus saprophyticus* is common in young women.

**Treatment**
■ Empiric treatment w/ciprofloxacin or TMP-SMZ
■ 3 days of abx Rx is as effective as longer courses of treatment for uncomplicated lower UTIs in women.
■ Treatment of asymptomatic bacteriuria in women w/diabetes is not indicated and does not appear to ↓ complications. Treatment is, however, indicated in pregnant pts, in those who are about to undergo urologic surgery, and in recipients of renal transplants soon after transplantation.
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381 UROLITHIASIS

Definition
Presence of calculi within the urinary tract. The 5 major types of urinary stones are Ca oxalate (>50%), Ca phosphate (10%-20%), uric acid (8%), struvite (15%), and cystine (3%).

Diagnosis
H&P
Stones may be asymptomatic or may cause the following signs and sx from obstruction:
- Sudden onset of flank tenderness
- N/V
- Pt in constant movement, attempting to lessen the pain (pts w/an acute abd are usually still because movement exacerbates the pain)
- Pain may be referred to the testes or labium (progression of stone down the urinary ureter)
- Fever and chills accompanying the acute colic if there is superimposed infection
- Pain may radiate anteriorly over to the abd and result in intestinal ileus.

Labs
- U/A: hematuria may be present; however, its absence does not exclude urinary stones. Evaluation of urinary pH is of value in identification of type of stone (pH >7.5 is associated w/struvite stones, whereas pH <5 generally is seen w/uric acid or w/cystine stones).
- Urine C&S should be obtained for all pts.
- Serum chemistries should include Ca, electrolytes, phosphate, and uric acid.
- Additional tests: 24-hr urine collection for Ca, uric acid, phosphate, oxalate, and citrate excretion is generally reserved for pts w/recurrent stones.

Imaging
- Plain films of the abd can identify radiopaque stones (Ca, uric acid stones).
- Renal sonography may be helpful.
- Intravenous pyelography demonstrates the size and location of the stone as well as degree of obstruction.
- Unenhanced (non–contrast-enhanced) helical CT scan does not require contrast media and can visualize the calculus (identified by the “rim sign” or “halo” representing the edematous ureteral wall around the stone). It is fast, is accurate (sensitivity 15%-100%, specificity 94%-96%), and readily identifies all stone types in all locations.

Etiology
- ↑ Absorption of Ca in the small bowel: type I absorptive hypercalciuria (independent of Ca intake)
- Idiopathic hypercalciuria nephrolithiasis is the most common dx for pts w/Ca stones; the dx is made only if there is no hypercalcemia and no known cause for hypercalciuria.
- ↑ Vitamin D synthesis (e.g., secondary to renal phosphate loss: type III absorptive hypercalciuria)
- Renal tubular malfunction w/inadequate reabsorption of Ca and resulting hypercalciuria
- Heterozygous mutations in the NPT2a gene result in hypophosphatemia and urinary phosphate loss
- Hyperparathyroidism w/resulting hypercalcemia
- ↑ Uric acid level (metabolic defects, dietary excess)
- Chronic diarrhea (e.g., IBD) w/↑ oxalate absorption
- Type 1 (distal tubule) renal tubular acidosis (<1% of Ca stones)
- Chronic hydrochlorothiazide treatment
- Chronic infections w/urease-producing organisms (e.g., Proteus, Providencia, Pseudomonas, Klebsiella). Struvite or Mg ammonium phosphate crystals are produced when the urinary tract is colonized by bacteria, producing ↑ concentrations of ammonia.
- Abnl excretion of cystine
- Chemotherapy for malignant neoplasms
**Treatment**

- ↑ in water or other fluid intake (doubling of previous fluid intake unless pt has h/o CHF or fluid overload)
- NI dietary Ca intake is recommended. If one does not consume enough Ca, less is available to bind to dietary oxalate; as a result, more oxalate reaches the colon, is absorbed into the bloodstream, and is excreted as Ca oxalate, setting the stage for Ca urolithiasis.
- Sodium restriction (to ↓ Ca excretion), ↓ protein intake to 1 g/kg/day (to ↓ uric acid, Ca, and oxalate excretion)
- ↑ in bran (may ↓ bowel transit time w/↑ binding of Ca and subsequent ↓ in urinary Ca)
- Pain control (use of narcotics is generally indicated because of the severity of pain)
- Specific Rx tailored to the stone type:
  - Uric acid calculi: control of hyperuricosuria w/allopurinol 100-300 mg/day; ↑ urinary pH w/potassium citrate, 10-mEq tablets tid
  - Ca stones:
    - Hydrochlorothiazide 25-50 mg qd in pts w/type I absorptive hypercalciuria
    - ↓ Bowel absorption of Ca w/cellulose phosphate 10 g/day in pts w/type I absorptive hypercalciuria
    - Orthophosphates to inhibit vitamin B synthesis in pts w/type III absorptive hypercalciuria
    - Potassium citrate supplementation in pts w/hypocitraturic Ca nephrolithiasis
    - Purine dietary restrictions or allopurinol in pts w/hyperuricosuric Ca nephrolithiasis
  - Struvite stones:
    - Most of the stones are large and cause obstruction and bleeding.
    - ESWL and percutaneous nephrolithotomy are generally necessary.
    - Prolonged use of abx directed against the predominant urinary tract organism may be beneficial to prevent recurrence.
    - Cystine stones: hydration and alkalization of the urine to pH >6.5, penicillamine, and tiopronin can also be used to ↓ the formation of cystine; captopril is also beneficial and causes fewer side effects.
- Surgical treatment in pts w/severe pain unresponsive to medication and pts w/persistent fever or nausea or significant impediment of urine flow:
  - Ureteroscopic stone extraction
  - ESWL for most renal stones
- The American Urological Association has issued the following guidelines for the treatment of ureteral stones:
  - Proximal ureteral stones <1 cm in diameter: options are ESWL, percutaneous nephroureterolithotomy, and ureteroscopy.
  - Proximal ureteral stones >1 cm in diameter: options are ESWL, percutaneous nephroureterolithotomy, and ureteroscopy. Placement of a ureteral stent should be considered if the stone is causing high-grade obstruction.
  - Distal ureteral stones <1 cm in diameter: most of these pass spontaneously. ESWL and ureteroscopy are 2 accepted modes of Rx.
  - Distal ureteral stones >1 cm in diameter: watchful waiting, ESWL, ureteroscopy (after stone fragmentation).

**Clinical Pearls**

- >50% of pts will pass the stone within 48 hr.
- Stones will recur in 50% of pts within 5 yr if no medical treatment is provided.

**VAGINITIS, FUNGAL**

**Definition**

Vaginal infection usually caused by *Candida albicans*. 
### Diagnosis

**H&P**
- Vaginal d/c (usually) or vulvar itching and irritation
- *Candida* vaginitis: suggested clinically by pruritus in the vulvar area together w/erythema of the vagina or vulva. A white d/c may be present.

**Labs**
- Wet preparation or Gram stain of the vaginal d/c under a microscope at low- and high-dry power. The yeast or pseudohyphae of *Candida* sp are more easily identified when 10% KOH is used in wet preparation.
- Culture for *T. vaginalis* or *Candida* sp: more sensitive than microscopic examination, but the specificity of culture for *Candida* sp to diagnose vaginitis is less clear.

### Treatment

- Fluconazole 150-mg PO tablet, single dose or
- Clotrimazole 500-mg vaginal tablet, one tablet single application, or
- Butoconazole 2% cream 5 g, intravaginally for 3 days

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### 383 VAGINITIS, TRICHOMONAS

**Definition**
Vaginal infection caused by the protozoan *Trichomonas vaginalis*.

**Diagnosis**
- Diffuse, malodorous, yellow-green d/c w/vulvar irritation
- Dx made by pH and microscopic examination of fresh samples of the d/c
- Examine the d/c: a cover slip is placed on each slide, and they are examined under a microscope at low- and high-dry power. The motile *T. vaginalis* are usually easily identified in the saline specimen.

**Treatment**
- Recommended regimen: metronidazole, 2 g PO in a single dose
- Alternative regimen: metronidazole, 500 mg twice qd for 7 days
- Treat both pt and sex partner.

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### 384 VAGINOSIS, BACTERIAL

**Definition**
Malodorous vaginal d/c that results from replacement of the nl H₂O₂-producing *Lactobacillus* sp in the vagina w/high concentrations of anaerobic bacteria (e.g., *Bacteroides* sp, *Mobiluncus* sp, *G. vaginalis*, and *Mycoplasma hominis*).

**Diagnosis**

**H&P**
- A homogeneous, white, noninflammatory d/c that smoothly coats the vaginal walls
- A fishy odor of vaginal d/c before or after addition of 10% KOH (whiff test)

**Labs**
- Presence of clue cells on microscopic examination
- pH of vaginal fluid >4.5
- When Gram stain is used, determination of the relative concentration of the bacterial morphotypes characteristic of the altered flora of bacterial vaginosis is an acceptable laboratory method for diagnosis of bacterial vaginosis.

**Treatment**
- Metronidazole, 500 mg PO bid × 7 days; or metronidazole gel 0.75%, one full applicator (5 g) intravaginally bid × 5 days; or clindamycin cream 2%, one full applicator (5 g) intravaginally at hs × 7 days
- Alternative regimens: metronidazole, 2 g PO in a single dose, or clindamycin, 300 mg PO bid × 7 days. Tinidazole (2 g qd × 2 days or 1 g qd × 5 days) is another treatment option.

**Clinical Pearls**
- Pts should be advised to avoid use of alcohol during treatment w/ metronidazole and for 24 hr thereafter.
- Clindamycin cream is oil based and may weaken latex condoms and diaphragms.
VENTRICULAR TACHYCARDIA (VT)

**Definition**
Three or more consecutive beats of ventricular origin (wide QRS) at a rate between 100 and 200 bpm (Fig. 3-48). When the QRS complexes of the VT are of the same shape and amplitude, the rhythm is termed *monomorphic VT*; when the QRS complexes vary in shape and amplitude, the rhythm is known as *polymorphic VT*. Polymorphic VT can be further subclassified on the basis of its association w/ nl or prolonged QT interval. Polymorphic VT occurring in the presence of a long QT is called *torsades de pointes*.

**Diagnosis**

**ECG**
Differentiation between ventricular beats and SVT w/aberrant ventricular conduction may be very difficult; because most wide-complex tachycardias are VT, wide-QRS tachycardia in the conscious adult should be considered VT until proved otherwise, especially in the presence of underlying heart disease.

- Factors favoring VT:
  - Morphology is similar to PVC.
  - Initiating event is a PVC.
  - Usually no response to vagal maneuvers
  - Presence of AV dissociation (P waves marching through QRS)
  - QRS duration >140 msec w/an RBBB pattern and >160 msec w/an LBBB pattern
  - Extreme LAD (<90 to ±180 degrees)
  - Combination of LBBB and RAD
  - Different QRS pattern during tachycardia compared w/a baseline ECG in pts w/preexisting BBB
  - QRS concordance (QRS waves are in same direction in all precordial leads)
  - Left peak (“rabbit ear”) of the QRS complex is taller than the right in lead V₁.
  - QS V₆

![monitor–continuous strip](image-url)
Diseases by autoimmune hematoproliferative It accompanied often a or FHx.

Treatment

An algorithm for dx and treatment of sustained monomorphic VT is described in Section 1 (ACLS algorithms).

Electrophysiologic mapping followed by surgical treatment can be performed for recurrent tachycardia, generally in combination w/CABG. The ACC and the AHA indications for Rx w/an automatic implantable cardioverter-defibrillator are as follows:

- Spontaneous sustained VT
- Cardiac arrest related to ventricular VF or VT not resulting from a transient or reversible cause
- Syncope of undetermined origin w клинически relevant, hemodynamically significant sustained VT or VF induced at EPS when drug Rx is ineffective, not tolerated, or not preferred
- Nonsustained VT w CAD, prior MI, LV dysfunction, and inducible VF or sustained VT at EPS that is not suppressed by a class I antiarrhythmic drug

386 VITAMIN K DEFICIENCY

Diagnosis

H&P

- May be asymptomatic w minor deficiency
- Bleeding complications may occur w severe deficiencies

Labs

- Prolonged PT (INR) that corrects after a 1:1 mix w nl pooled plasma

Etiology

- Vitamin K deficiency may be due to malabsorption syndromes (often due to abx), liver disease (↓ stores), poor dietary intake, and hereditary combined deficiencies of the vitamin K-dependent proteins, including prothrombin, factor VII, factor IX, and factor X. Vitamin K antagonists (warfarin, rodenticides) can lead to prolonged and life-threatening bleeding.

Treatment

- Mild deficiency: daily doses of PO vitamin K1 100-150 mg. PT (INR) begins to normalize after 12 hr and should normalize completely in 48 hr. Vitamin K can also be given SC (poorly absorbed in edematous pts) and IV (risk of anaphylaxis).
- In pts w severe deficiency and active bleeding or requiring invasive procedures, the administration of vitamin K should be preceded by the infusion of FFP (2-3 units [400-600 mL]). With significant PT prolongation and severe bleeding, up to 15 mL/kg may be needed. Measurement of PT and APTT should be obtained after the initial FFP infusion to determine need for additional infusions.

387 VON WILLEBRAND DISEASE (VWD)

Definition

Congenital disorder of hemostasis characterized by defective or deficient vWF. There are several subtypes of vWD. The most common type (80% of cases) is type I, which is caused by a quantitative ↓ in vWF; type IIA and type IIB are results of qualitative protein abnormalities; type III is a rare autosomal recessive disorder characterized by a nearly complete quantitative deficiency of vWF.

Acquired vWD is a rare disorder that usually occurs in elderly pts and usually is manifested w mucocutaneous bleeding abnormalities and no clinically meaningful FHx. It is often accompanied by a hematoproliferative or autoimmune
disorder. Successful treatment of the associated illness can reverse the clinical and laboratory manifestations.

**Diagnosis**
- Initial testing includes PTT (↑), platelet count (nl), and bleeding time (†).
- Subsequent tests include vWF level (↓), factor VIII:C (↓), and ristocetin agglutination (↑) in type IIB.
- Type IIA vWD can be distinguished from type I by absence of ristocetin cofactor activity and abnormal multimer.
- Type IIB vWD is distinguished from type I by abnl multimer.

**Treatment**
- Desmopressin acetate (DDAVP) to cover minor procedures and traumatic bleeding in mild type I vWD. Dose is 0.3 μg/kg in 100 mL of NS IV infused >20 min. DDAVP is also available as a nasal spray (dose of 150 μg spray administered to each nostril) as a preparation for minor surgery and management of minor bleeding episodes. DDAVP is not effective in type IIA vWD and is potentially dangerous in type IIB (↑ risk of bleeding and thrombocytopenia).
- In pts w/severe disease, replacement Rx in the form of cryoprecipitate is the method of choice. The standard dose is 1 bag of cryoprecipitate per 10 kg of BW.
- Factor VIII concentrate rich in vWF (Humate-P) is useful to correct bleeding abnormalities.
- Life-threatening hemorrhage unresponsive to Rx w/cryoprecipitate or factor VIII concentrate may require transfusion of nl platelets.

### 388 WALDENSTRÖM’S MACROGLOBULINEMIA

**Definition**
Plasma cell dyscrasia characterized by the presence of ↑ blood concentration of monoclonal immunoglobulin (IgM).

**Diagnosis**

**H&P**
- Weakness, fatigue, weight loss, fever, night sweats
- Easy bleeding, bruising
- Headache, dizziness, vertigo, deafness, and seizures (hyperviscosity syndrome)
- Fever, night sweats
- Exam: ecchymoses, purpura, hepatomegaly, splenomegaly, symmetric peripheral neuropathy

**Labs**
- CBC w/diff: anemia; WBC count usually nl; thrombocytopenia may occur.
- Peripheral smear: may reveal “stacked coin” rouleaux formations and malignant lymphoid cells in terminal pts.
- ↑ ESR, cryoglobulins, RF, or cold agglutinin may be present.
- SPEP: homogeneous M spike (monoclonal gammopathy).
- Immunoelectrophoresis confirms IgM responsible for the M spike.
- Urine IEP: monoclonal light chains are usually κ chains. Bence Jones protein can be seen but is not the typical finding in Waldenström’s macroglobulinemia.
- IgM levels are ↑, generally >3 g/dL.
- β2-Microglobulin: ↑ in 55%; high levels are associated w/poor prognosis.
- Serum viscosity: sx usually occur when the serum viscosity is 4× nl; classic feature, although present in only 15% of cases.
- Bone marrow: lymphoplasmacytoid cells are characteristic.

**Imaging**
- CXR to r/o pulmonary involvement

**Treatment**
- Plasmapheresis to alleviate sx of hyperviscosity
- Treatment of lymphoproliferative disorder: single or combination Rx (e.g., rituximab and nucleoside analogues, nucleoside analogues and chlorambucil, CHOP)
- Other treatment options: interferon alfa, thalidomide, and autologous SCT
Clinical Pearls
- Median survival is 4-5 yr. 10% achieve complete remission.
- Neg impact on survival: age >65 yr, male gender, presence of organomegaly, cytopenias.

389 WARFARIN SKIN NECROSIS
Definition
Lesions that follow warfarin Rx, occurring in 0.01%-0.1% of all pts receiving warfarin. Believed to be due to rapid depletion of protein C.

Diagnosis
- Lesions usually appear 3-6 days after initiation of Rx.
- Skin necrosis begins suddenly as painful erythematous patches that become edematous and indurated and rapidly progress to irregularly hemorrhagic and necrotic plaques, nodules, and bullae. Large tumid indurations and infarcts eventually occur w/eschar formation and sloughing.
- The lesions often develop in the skin overlying fatty areas, such as buttocks, thighs, and breasts.

Etiology
- Pts who are deficient in protein C are at high risk because the disorder is thought to be due to a temporary imbalance between the procoagulant and vitamin K factors.

Clinical Pearl
- Can be prevented by avoiding ↑ loading doses of warfarin and achieving therapeutic anticoagulant levels w/UFH or LMWH.

390 WEGENER’S GRANULOMATOSIS
Definition
Multisystem disease generally consisting of the classic triad of
- Necrotizing granulomatous lesions in the upper or lower respiratory tracts
- Generalized focal necrotizing vasculitis involving both arteries and veins
- Focal GN of the kidneys
  “Limited forms” of the disease can also occur and may evolve into the classic triad; Wegener’s granulomatosis can be classified by the “ELK” classification, which identifies the three major sites of involvement: E, ears, nose, and throat or respiratory tract; L, lungs; K, kidneys.

Diagnosis
H&P
- Clinical manifestations often vary w/the stage of the disease and degree of organ involvement.
- Frequent manifestations are
  - Upper respiratory tract: chronic sinusitis, chronic otitis media, mastoiditis, nasal crusting, obstruction and epistaxis, nasal septal perforation, nasal lacrimal duct stenosis, saddle nose deformities (resulting from cartilage destruction)
  - Lung: hemoptysis, multiple nodules, diffuse alveolar pattern
  - Kidney: renal insufficiency, GN
  - Skin: necrotizing skin lesions
  - Nervous system: mononeuritis multiplex, cranial nerve involvement
  - Joints: monarthritis or polyarthritis (nondeforming), usually affecting large joints
  - Mouth: chronic ulcerative lesions of the oral mucosa, “mulberry” gingivitis
  - Eye: proptosis, uveitis, episcleritis, retinal and optic nerve vasculitis

Labs
- Positive test result for cytoplasmic pattern of ANCA (cANCA)
- Other labs: anemia, leukocytosis, hematuria, RBC casts, and proteinuria; ↑ serum Cr, ↓ CrCl, ↑ ESR, + RF, and ↑ CRP
- Bx of one or more affected organs should be attempted; the most reliable source for tissue dx is the lung. Lesions in the nasopharynx (if present) can be easily sampled.
**Imaging**
- CXR: bilateral multiple nodules, cavitated mass lesions, pleural effusion (20%)
- PFTs: useful in detecting stenosis of the airways

**Treatment**
- Prednisone 60-80 mg/day and cyclophosphamide 2 mg/kg. Once the disease comes under control, prednisone is tapered and cyclophosphamide is continued. Other potentially useful agents in pts intolerant of cyclophosphamide are azathioprine, MTX, and mycophenolate mofetil.
- TMP-SMX: useful alternative in pts w/lesions limited to the upper or lower respiratory tracts in absence of vasculitis or nephritis. Treatment w/TMP-SMX (160 mg/800 mg bid) also ↓ the incidence of relapses in pts w/Wegener’s granulomatosis in remission. It is also useful in preventing *Pneumocystis* pneumonia, which occurs in 10% of pts receiving induction Rx. When used for prophylaxis, dose of TMP-SMX (160 mg/800 mg) is 1 tablet 3×/wk.

**Clinical Pearls**
- cANCA levels should not dictate changes in Rx because they correlate erratically w/disease activity.
- The incidence of venous thrombotic events in Wegener’s granulomatosis is significantly higher than in the general population.

## Wernicke’s Encephalopathy

### Definition
Syndrome of acute extraocular muscle dysfunction, confusion, and ataxia resulting from thiamine deficiency.

### Diagnosis
**H&P**
- Disturbance of extraocular motility, including nystagmus, abducens nerve palsy, and disorders of conjugate gaze
- Encephalopathy
- Ataxia of gait
- Peripheral neuropathy may be seen in addition to these typical findings.

**Labs**
- CBC
- Serum chemistries
- Serum pyruvate is elevated.
- Whole-blood or erythrocyte transketolase is ↓; rapid resolution to nl in 24 hr w/thiamine repletion.

### Imaging
- MRI brain: may show diencephalic and mesencephalic lesions acutely, but there is no definitive radiologic study for dx.
- CT brain: may show cerebral atrophy from chronic alcoholism.

### Etiology
- Thiamine deficiency from alcohol abuse or other malnourished state

### Treatment
- 100 mg thiamine IV or IM immediately. Typically, thiamine IV for 3-5 days, then oral.
- Avoid dextrose-containing fluids until thiamine is repleted.
- Prophylactic treatment for delirium tremens if alcoholic.
- Attempt to treat alcoholism or underlying malnourished state.
- Chronic oral thiamine repletion; typical dose: 5 mg/day.
- Case reports suggest that donepezil may help chronic memory problems.

## Wilson’s Disease

### Definition
Hereditary disorder (autosomal recessive) of copper transport w/inadequate biliary copper excretion, leading to an accumulation of the metal in liver, brain, kidneys, and corneas. The gene for Wilson’s disease is located on chromosome 13.
### Diagnosis

**H&P**

- **Hepatic presentation:**
  - Acute hepatitis w/malaise, anorexia, nausea, jaundice, elevated transaminase, prolonged PT; rarely fulminant hepatic failure
  - Chronic active (or autoimmune) hepatitis w/fatigue, malaise, rashes, arthralgia, ↑ transaminase, ↑ serum IgG, + ANA and anti-smooth muscle Ab
  - Chronic liver disease/cirrhosis w/hepatosplenomegaly, ascites, low serum alb, prolonged PT, portal HTN

- **Neurologic presentation:**
  - Movement disorder: tremors, ataxia
  - Spastic dystonia: masklike facies, rigidity, gait disturbance, dysarthria, drooling, dysphagia

- **Psychiatric presentation:** depression, obsessive-compulsive disorder, psychopathic behaviors

- **Other organs:**
  - Hemolytic anemia
  - Renal disease (i.e., Fanconi’s syndrome w/hematuria, phosphaturia, renal tubular acidosis, vitamin D–resistant rickets)
  - Cardiomyopathy
  - Arthritis
  - Hypoparathyroidism
  - Hypogonadism

- **Physical findings:**
  - Ocular: the Kayser-Fleischer ring is a gold-yellow ring seen at the periphery of the iris
  - Stigmata of acute or chronic liver disease
  - Neurologic abnormalities: see previous

### Labs

- Abnl LFTs (AST > ALT)
- ↓ Serum ceruloplasmin level (<200 mg/L)
- ↓ Serum copper (<65 µg/L)
- 24-hr urinary copper excretion >100 µg (nl <30 µg); ↑ to >1200 µg/24 hr after 500 mg of D-penicillamine (nl <500 µg/24 hr)
- ↓ Serum uric acid and phosphorus
- Abnl U/A (hematuria)
- Coombs’ – hemolytic anemia

### Bx Findings

- Early: steatosis, focal necrosis, glycogenated hepatocyte nuclei; may reveal inflammation and piecemeal necrosis
- Late: cirrhosis
- Hepatic copper content (>200 mg/g of dry weight; nl is 20-50 mg/g)

### Treatment

- Penicillamine (chelator Rx): 0.75-1.5 g/day divided bid (w/pyridoxine 25 mg/day)
- Trientine (triethylene tetramine) (chelator Rx): 1-2 g/day divided tid. Monitor CBC.
- Zinc (inhibits intestinal copper absorption): 50 mg tid. Monitor zinc level.
- Ammonium tetrathiomolybdate for neurologic sx
- Antioxidants
- Liver transplantation (for severe hepatic failure unresponsive to chelation)

#### Wolff-Parkinson-White Syndrome (WPW)

**Definition**

ECG abnormality associated w/earlier than nl ventricular depolarization following the atrial impulse and predisposing the affected person to tachyarrhythmias.
WPW Preexcitation

- Short PR
- Wide QRS
- Delta wave (arrow)

**FIGURE 3-49.** Preexcitation through the bypass tract in WPW syndrome is associated with the triad of findings shown here.

**Diagnosis**

**ECG** (Fig. 3-49)

Three basic features characterize the ECG abnormalities in WPW syndrome:

- PR interval <120 msec
- QRS complex >120 msec w/a slurred, slowly rising onset of QRS in some leads (delta wave)
- ST-T wave changes

**Etiology**

- Existence of accessory pathways (Kent bundles)

**Treatment**

- No treatment in the absence of tachyarrhythmias
- Symptomatic tachyarrhythmia Rx
- Acute episode: adenosine, verapamil, or diltiazem to terminate an episode of reciprocal tachycardia
- Digitalis should not be used because it can ↓ refractoriness in the accessory pathway and accelerate the tachycardia.
- Cardioversion should be used in the presence of hemodynamic impairment.

**Credits**

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